MAY 16 1944

Vol. 207, No. 5 MAY, 1944 No. 866

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

REG. U. S. PAT. OFF.

Editor:
E. B. KRUMBHAAR, M.D.

Acting Assistant Editor:
WILLIAM C. STADIE, M.D.

Established 1820

Medical Library

CLINICAL ASPECTS OF PAIN IN THE CHEST. I. ANGINA PECTORIS. By TINSLEY R. HARRISON. 561

INFARCTION OF THE LATERAL WALL OF THE LEFT VENTRICLE. PATHOLOGIC AND ELECTROCARDIOGRAPHIC STUDY. By HUGO WARNEFORD THOMSON, M.D., and HAROLD FEIL, M.D. 588

ABDOMINAL AORTIC ANEURYSM. RUPTURE INTO THE JEJUNUM PRECEDED BY OCCULT BLOOD IN THE STOOL. By GLENN I. HILLER, M.D., and RICHARD M. JOHNSON, M.D. 600

A TEST FOR VASCULAR TONE IN HUMANS AND ITS APPLICATION TO THE STUDY OF VASCULAR DISEASES WITH SPECIAL REFERENCE TO THE ETIOLOGY AND PREVENTION OF THROMBOPHLEBITIS. By MEYER NAIDE, M.D., with the technical assistance of ANN SAŸEN. 606

ACUTE THROMBOCYTOPENIC PURPURA IN INFECTIOUS MONONUCLEOSIS. REPORT OF A CASE. By PUTNAM C. LLOYD, Major, M.C., A.U.S. 620

THE "HEAT RESISTANCE" OF ERYTHROCYTES. A SPECIFIC TEST FOR THE RECOGNITION OF MARCHIAFAVA'S ANEMIA. By ROBERT HEGGLIN, M.D., and CONRAD MAIER, M.D. 624

HOMOLOGOUS SERUM JAUNDICE. A REVIEW OF THE LITERATURE AND REPORT OF A CASE. By LIEUT. JOHN R. NEEFE, M.C., A.U.S., T. GRIER MILLER, M.D., and FRANCIS W. CHORNOCK, Ph.D. 626

BLOOD STUDIES IN ALLERGY. II. THE PRESENCE IN ALLERGIC DISEASE OF ATYPICAL LYMPHOCYTES AND SYMPTOMS SUGGESTING THE RECOVERY PHASE OF INFECTIOUS MONONUCLEOSIS. By THERON G. RANDOLPH, M.D., and ELIZABETH BARBER GIBSON. 638

RELATIONSHIP OF LYMPHOGRANULOMA VENEREUM INFECTION TO THE INCIDENCE OF HYPERGLOBULINEMIA. By PAUL B. BEESON, M.D., and EDWARD S. MILLER, M.D. 643

CHLOROPHYLL: AN EXPERIMENTAL STUDY OF ITS WATER-SOLUBLE DERIVATIVES. I. REMARKS UPON THE HISTORY, CHEMISTRY, TOXICITY AND ANTIBACTERIAL PROPERTIES OF WATER-SOLUBLE CHLOROPHYLL DERIVATIVES AS THERAPEUTIC AGENTS. By LAWRENCE W. SMITH, M.D. 647

A TUMOR OCCURRING IN THE SUPERIOR PULMONARY SULCUS. By I. IMBER, M.D. . 654

PROGRESS OF MEDICAL SCIENCE:

THERAPEUTICS: PENICILLIN. A REVIEW OF THE LITERATURE THROUGH 1943. By LIEUT. G. F. SCHMITT, M.C., U.S.N.R. 661

RADIOLOGY: A NEW CHOLECYSTOGRAPHIC MEDIUM. By H. M. WEBER, M.D. . 678

PROCEEDINGS OF THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA . . . 684

Contents continued on adv. page 10

OWNERS AND PUBLISHERS LEA & FEBIGER PHILADELPHIA 6, PENNA.

COPYRIGHT, 1944, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER

PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR

Lowering blood pressure of hypertensive patients must be done safely to avert fatalities. Sustained effect and low toxicity should characterize the medication employed, qualities difficult to achieve with the nitrites and barbiturates respectively.

HEPVISC has proved a valuable hypotensive, with extensive clinical use. Not only does it bring blood pressure down in a gradual manner, but its effect is sustained. Striking relief of hypertensive symptoms such as headaches, dizziness and tinnitus also ensue with the administration of **HEPVISC** in well over 80% of cases.

Each **HEPVISC** Tablet contains Viscum album extract 50 mg., hepatic desiccated substance 60 mg. and insulin-free pancreatic desiccated substance 60 mg.

INDICATIONS: Essential hypertension, benign hyperpiesia, fibrotic kidney and hypertension accompanying pregnancy.

DOSAGE: Average dose is 3 to 6 tablets daily, in divided doses ½ hour before meals. Continue treatment for 2 to 3 weeks with a week's interval between courses.

Bottles of 50 and 500 tablets.

Liberal samples to physicians on request.

HEPVISC

AN EFFECTIVE HYPOTENSIVE

ANGLO-FRENCH LABORATORIES, INC.

75 VARICK STREET, NEW YORK 13, N. Y.

THE AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

MAY, 1944

ORIGINAL ARTICLES

CLINICAL ASPECTS OF PAIN IN THE CHEST

I. ANGINA PECTORIS

BY TINSLEY R. HARRISON
WINSTON-SALEM, N. C.

(From the Department of Internal Medicine of the Bowman Gray School of Medicine of Wake Forest College)

THORACIC distress is a common complaint. Thus, of the past 200 adult, non-obstetrical patients admitted to the North Carolina Baptist Hospital, 55 have complained of pain in the abdomen, 28 of pain in the chest, and 20 of pain in the head. When only patients admitted to the medical service are considered, the corresponding figures are 57, 50 and 38, respectively. It may be stated, therefore, that pain in the region of the chest is present in 15 to 25% of all adult patients who are sufficiently ill to need hospitalization, and that discomfort in this area is probably more common than in any other region of the body except the abdomen.

The majority of conditions which cause pain in the chest are either of serious nature or of trifling significance. Unfortunately, the differentiation between the two groups of disorders, though sometimes easy, is often difficult and occasionally well-nigh impossible. Hence, disastrous mistakes in treatment and embarrassing errors in prognosis are frequently made. In view of the puzzling manifestations and frequent occurrence of this symptom a study has been made of a large group of patients with chest pain.

The investigation, of which the present report is the first part, has lasted for a number of years and has dealt with several hundred patients. A complete history and physical examination have been made in all cases, and electrocardiograms and roentgenologic studies have been carried out in most of them. Additional investigations have been made when indicated. As the study has progressed it has become more and more apparent that the history is, in most patients, the single most important method of examination, and in many patients is more important than all other procedures combined. Therefore, especial emphasis has been placed on an attempt to analyze the subjective aspects of chest pain.

Methods. Most of the patients have been observed by the author personally, many of them on the wards of the North Carolina Baptist Hospital. Some have been seen in consultation, and a small number of the cases analyzed have been taken from records which were kindly loaned by professional colleagues. Since the purpose of the study has been primarily to try to assist in developing better criteria for separating the pain due to disturbance in the coronary circulation from that due to other disorders, patients with pain limited to the back of the chest and those with discomfort due to pleurisy brought about by acute infections have been omitted from the series. A few patients with pain limited to the shoulders or arms have been included, even when there was no pain in the chest.

The method of study has consisted of an unusually careful analysis of the pain, including detailed questioning concerning location, radiation, duration, intensity, quality, and above all, concerning the relationship of the pain to various body functions. A given patient's pain has been classified and put into a special category only when the causation of the pain has seemed to be determined with reasonable accuracy, as the result of all the studies made of the patient. In many instances it has not been possible to make a satisfactory diagnosis; some of the most baffling and interesting cases have remained puzzles and hence are not included in the series.

Angina pectoris has been selected as the subject of the first report, not only because this disorder embraced the largest single group of patients, but also for the purpose of obtaining a standard for comparison with other disorders causing pain which may to some extent simulate that due to coronary disease. Since the term "angina pectoris" is still used somewhat differently by various authors, it may be well to define at the beginning the meaning attached to it in this communication. By the term "angina pectoris," I refer to a condition characterized by recurrent attacks of discomfort in or near the chest, commonly induced by conditions which impose an additional burden on the heart, ordinarily dependent on disturbance of the oxidative processes in the myocardium and always attended by the likelihood of sudden death. Hence, pain due to myocardial infarction is excluded from consideration in this report. Certain patients with angina pectoris, as herein defined, have likewise been omitted. Thus, subjects with anginal attacks occurring as prodromal events prior to myocardial infarction, and patients with "status anginosus" are not included. These acute conditions, although falling within the category of angina pectoris, may be more properly studied in relation to myocardial infarction, with which they are closely allied, rather than in connection with the ordinary form of angina pectoris, which is a much more chronic disorder.

Since, according to the definition which has been given, the anginal syndrome is delimited in terms of clinical and functional rather than structural criteria, a critical reader will feel justified in entertaining some question as to the accuracy of the diagnosis. Granting the likelihood that a few of the patients included in the series may have been erroneously considered to have been suffering from angina pectoris, it seems improbable that the percentage of diagnostic error could be large. The reasons for this statement are as follows:

1. Of the 77 patients with whom this reports deals, 34 presented the picture of myocardial infarction either prior to or—more commonly—subsequent to the development of angina pectoris.

2. The manner of death of the 13 patients in the series who are known to be dead was such as to support the diagnosis of angina pectoris. Thus:

(*a*) Of 8 patients who died outside the hospital
  (1) Four died suddenly while in their usual state of health.
  (2) Two died during typical status anginosus.
  (3) One died suddenly following myocardial infarction.
  (4) One committed suicide several weeks after myocardial infarction.
(*b*) Of 5 patients who died in the hospital:
  (1) One died as the result of embolism following coronary thrombosis, no autopsy being done.
  (2) Autopsy revealed extensive disease of the coronary arteries in the remaining subjects.

Since the criteria employed for the diagnosis of angina pectoris were the same in the remaining subjects as in these 13 individuals, it is perhaps safe to assume that complete data would eventually reveal a similarly high incidence of sudden death and of coronary disease.

3. During the period in which these 77 patients were being studied there were: (*a*) Only 3 cases diagnosed as angina pectoris in which the subsequent clinical course was such as to cause this diagnosis to be changed. (*b*) Only one patient in whom at autopsy the diagnosis was not supported. (This patient had rupture of an aortic aneurysm but no significant coronary disease and no lesion of the aortic valves.) These 4 cases are not included in the series.

These observations lead to the conclusion that the percentage of erroneous diagnoses in the series is small, probably smaller than in the case of most conditions in which the diagnosis is based on clinical findings alone.

Etiologic Factors. The data listed in Table 1 are not materially different from those found in the publications of others, in that the predominance of males and of patients over the age of 50—both points stressed by Heberden in his original description[16]—are well illustrated. The generally accepted outstanding significance of disease of the coronary arteries is illustrated in the Table, as is the importance of diseases of the aortic valve, which was stressed by Keefer and Resnik.[18] The 3 patients who had no evidence of structural cardiac disease are of particular interest and will be discussed in some detail later. Since the etiologic factors were, in general, those which are generally recognized in the literature, they need not be considered further.

Analysis of the Pain. The data presented in Table 2 are largely self-explanatory. *Localization* of the distress in the substernal region, which has been emphasized as one of the most common features of the disease,[3] was far from a constant feature, being present in only a little more than half the patients. Many of the subjects complained of pain situated chiefly in the precordial area just to the left of the sternum. Abdominal localization of the pain was less frequent than some authors have indicated, and a number of the patients who on first being questioned stated that the pain was in the abdomen, were found on more careful questioning to have pain in the retro-xyphoid region. Pain in the region of the umbilicus or below it was not encountered in any

subject and the 4 patients who had definite epigastric localization of the pain also had discomfort in the chest or arms. In not one patient, therefore, was the pain exclusively abdominal. This point may perhaps be of some value in differential diagnosis. Several of the patients with precordial pain had discomfort in the region of the apex but not a single individual complained of pain entirely limited to the periapical area. Discomfort in the mid- or posterior axillary region was not encountered and no patient had pain in the right side of the back of the chest or in the flank. The rarity of pain in the region of the left costal margin is noteworthy. Perhaps the most confusing patients were the 2 who had pain limited to the back of the neck. The other 4 patients with pain in the back of the neck also had pain in the chest or arms.

TABLE 1.—ETIOLOGIC DATA IN 77 PATIENTS WITH ANGINA PECTORIS

	No. of cases	%
I. *Sex*		
Males	58	75.3
Females	19	24.7
II. *Age*		
20–29	3	3.9
30–39	5	6.5
40–49	9	11.7
50–59	26	33.7
60–69	27	35.1
70–79	7	9.1
III. *Underlying Disease Process*		
Coronary arteriosclerosis (presumptive or proven)	64	83.1
Lesions of aortic valve:		
Rheumatic	4	5.2
Calcareous	2	2.6
Syphilitic	1	1.3
Syphilitic aortitis and (presumptive) ostial stenosis	1	1.3
Thrombo-angiitis obliterans	2	2.6
No evidence of structural cardiac disease:		
Hypoglycemia	2	2.6
Hypochromic anemia	1	1.3

The lack of sharp localization which, as stressed by Lewis,[20] is a feature of pain arising from visceral structures, was noted in most of the patients. This point is of some value in differentiating the pain of angina pectoris from that of cardiac neurosis, as has been pointed out by Goodrich and Keyes.[12] Eleven subjects stated that the point of greatest intensity was extrathoracic, but in only 5 of these was there a complete absence of substernal or precordial discomfort. Such cases, with pain limited to extrathoracic areas, have been recently studied by Spillane and White,[25] who found that, after varying periods of time, pain in the chest developed in each of their 12 patients who originally had the pain of effort only in the arms. In recent years increasing evidence has accumulated indicating that the cardiac afferent pathways may be more numerous and widespread than was formerly believed, and suggesting that various accessory pathways may be responsible for the bizarre distribution of the pain often encountered in patients with angina pectoris.[1,5,22]

The chief points of interest in regard to the *duration* of the pain were the rarity of pain lasting for more than 30 minutes, and of discomfort enduring for only a few seconds. There were 3 patients who originally stated that their pain lasted for a fraction of a minute only, but when pain produced under observation by exercise was timed, it was found to last for a minute or longer in each instance. The 3 patients who complained of pain lasting for days at a time all admitted having paroxysmal exacerbations which were brought on by the usual precipitating factors and which lasted only a few minutes. Perhaps these patients had the so-called myocardial fatigue pain plus angina pectoris, but if so, they were unable to distinguish the two pains from each other in respect to location and quality.

In the case of the subject who claimed to have attacks lasting from 1 to 2 hours, the situation was complicated by the existence of a well-marked anxiety state as well as attacks of paroxysmal tachycardia, either of which may have caused precordial pain for a considerable period of time. However, she claimed that nitroglycerine relieved these pains as well as the more common and shorter anginal attacks produced by effort or emotion. The patient with attacks due to paroxysmal auricular fibrillation also had frequent attacks of shorter duration brought on by effort. Of the 3 persons with attacks due to hypoglycemia and lasting 30 minutes to 1 hour, one had frequent attacks of shorter duration appearing with effort. The other 2 had no attacks with effort and apparently in these instances hypoglycemia was the sole precipitating factor, the patients being free from any signs of structural cardiac disease. These subjects will be discussed in more detail later.

The tendency of anginal attacks to last for only a few minutes was mentioned by Heberden,[16] and its diagnostic significance has recently been reëmphasized by Barnes and Pruett.[3] Subject to the error inherent in all generalizations, it may be stated that a pain lasting for only a few seconds or for more than an hour is not likely to be due to angina pectoris.

The data as regards *intensity* of pain are somewhat at variance with widely accepted concepts. Severe pain was rare in this series. In approximately half the patients pain was either mild or minimal (*i. e.*, barely perceptible). Most such patients did not seek medical advice because of pain in the chest but because of some other complaint such as hypertension, and in these subjects with mild pain the presence of angina pectoris was demonstrated only as a result of careful questioning. However, mildness of the pain does not in any sense speak against angina pectoris. One of the patients with pain of minimal severity expired suddenly when apparently in his usual health, and another who died some years later of cerebral hemorrhage was found at autopsy to have well marked coronary sclerosis. Unless the physician makes a deliberate attempt to inquire carefully about minor chest discomfort appearing with effort and lasting a few minutes in all patients beyond the age of 50—whether or not such a complaint is offered voluntarily—

he will overlook a large percentage of the individuals with angina pectoris.

TABLE 2.—ANALYSIS OF PAIN IN 77 PATIENTS WITH ANGINA PECTORIS

I. *Location and, or, Radiation*

	No. of cases	%
Substernal	42	54.5
Precordial	30	39.0
Left arm (including shoulder and hand)	23	29.9
Front of neck	14	18.2
Both arms	12	15.6
Retro-xyphoid	6	7.8
Back of neck	6	7.8
Back of left side of chest	5	6.5
Epigastrium	4	5.2
Left pectoral	3	3.9
Right arm (including shoulder and hand)	2	2.6
Jaw	1	1.3
Left anterior costal margin	1	1.3

Note absence of pain limited to periapical region or axillæ, or localized in right side of back or abdomen, lower abdomen, lower back or flanks.

II. *Duration*

	No. of cases	%
Less than 1 minute	0	0
1 to 30 minutes	69	89.6
30 to 60 minutes	4*	5.2
1 to 2 hours	1†	1.3
Days or weeks	3‡	3.9

* Three cases had hypoglycemia—1 had paroxysmal auricular fibrillation.
† Paroxysmal tachycardia and cardiac neurosis in addition to effort angina.
‡ Dull, steady pain with exacerbations lasting a few minutes.

III. *Intensity*

	No. of cases	%
Minimal	7	9.1
Mild	31	40.2
Moderate	22	28.6
Severe	10	13.0
Variable	7	9.1

IV. *Character*

Constrictive*	31	40.2
Aching	15	19.5
Burning	4	5.2
Numbness only	1	1.3
Lancinating	1†	1.3
Throbbing	0	0
Vague	25	32.5

* Including "squeezing," "tight," "cramping," "heavy," "pressing," etc.
† This patient had pain in the chest from gall-bladder disease as well as from angina pectoris.

The data as regards the *character* of the pain are not very satisfactory in that one-third of the patients were unable to describe this feature accurately. (In order to avoid obtaining a misleading description of the pain the patients were given a list of descriptive terms, such as "stabbing," "shooting," "burning," "squeezing," "grasping," "gripping," "aching," "throbbing," "pressing," "heavy," and so forth, and

allowed to choose the term which best described the discomfort.) As would be expected, the most frequent descriptive term chosen was one which fell under the general category of constrictive or "pressing" pain. However, about one-fifth of the patients described the discomfort as consisting of a dull ache, and several individuals insisted that the pain consisted of a feeling of warmth. This is of interest in view of the observations of Lewis,[20] which indicate that pain having a burning quality arose only in superficial tissues of the body and never in the internal organs. In 12 patients the sensation of pressure or aching in the chest was accompanied by numbness in other parts, particularly in the arms or fingers. One patient, whose discomfort was limited to the left arm, complained only of a sensation of numbness. From a diagnostic standpoint it is perhaps of interest that no patient described the pain as being synchronous with the heart beat, *i. e.*, of throbbing character, and that the only patient who claimed to have lancinating ("stabbing," "shooting," "cutting" or "sticking") pain also had gallbladder disease producing pain in the left side of the chest. It is possible that this individual may have confused the pain from the two different disorders, but opportunity to question him when the pain was present did not occur. In addition there were 4 patients who complained of pain of stabbing quality, who are not included in the series because these individuals did not sufficiently fulfill the criteria for the diagnosis of angina pectoris. They are regarded as suspicious cases of the disorder and are being followed. Thus far, none of them has developed unequivocal evidence of the disease. Hence, these individuals are not included in the series. In any case, it may be stated that pain of lancinating character either does not occur at all, is due to associated disorders, or is at least very rare as a result of angina pectoris.

Relation of the Pain to Various Body Functions. A. Position. No patient noted that the standing or sitting postures tended to induce the pain. However, there were 11 individuals in whom the attacks of pain seemed to bear a definite relationship to the recumbent position (Table 3, part I). All of these subjects gave a story of pain on effort. In addition they had attacks of pain which came on frequently in the recumbent posture while at rest, but did not tend to have attacks coming on at rest while sitting upright or standing. Two of these 11 subjects also noted that when sitting in a slumped posture with the feet elevated the attacks tended to come on just as they did during recumbency. There were likewise 2 patients who had attacks of pain with effort due to angina pectoris, and attacks of pain when lying down, due to hiatal hernia. One of these patients was able to distinguish between the character and location of the pain. The other individual could make no such distinction, stating that the pain due to the two conditions was identical in distribution and in character.

As an example of the rather striking relationship which exists in certain patients between anginal attacks and the recumbent posture, the following cases may be cited.

TABLE 3.—RELATION OF THE PAIN TO VARIOUS BODY FUNCTIONS IN 77 PATIENTS WITH ANGINA PECTORIS

I. *Position as Factor in Inducing Attacks*

	No. of cases	%
Standing	0	0
Sitting (upright)	0	0
Sitting (slumped)	2	2.6
Recumbent*	11†	14.2

* One patient had aggravation by lying on left side with partial relief on turning to right side.

† These patients experienced partial to complete relief by changing to standing or sitting position.

II. *Pain Induced by General Exertion*

	No. of cases	%
General exertion*	70	90.8

* The patients with pain not related to effort included (1) 2 patients with hypoglycemia; (2) 2 patients with ectopic tachycardia; (3) 2 patients who led unusually sedentary lives; (4) 1 patient who was almost bedridden by thrombo-angiitis obliterans.

III. *Pain Induced by Specific Local Muscular Movements*

	No. of cases	%
Specific local muscular movements	8*	10.4

* These patients had "coronary shoulder pain" in addition to angina on effort.

IV. *The Alimentary Tract in Relation to Anginal Attacks*

	No. of cases	%
A. Functions tending to precipitate pain:		
Swallowing*	2	2.6
Eating:		
Alone†	6	7.8
Plus exertion‡	17	22.0
Constipation	1§	1.3
B. Functions tending to relieve pain:		
Eating‖	12	15.5
Vomiting	1¶	1.3
Belching	7	9.1
Expulsion of flatus	2	2.6

* The pain due to swallowing was caused by esophageal spasm in 1 patient and by cascade deformity of the stomach in the other.

† One of these patients did not have pain on effort—he took practically no exercise. The remainder had typical effort angina and also attacks at rest after meals.

‡ Less exertion was required to induce attacks after meals than at other times.

§ Attacks more readily provoked when constipated.

‖ Attacks most frequent 3 to 5 hours after meals, occurring with less effort—3 patients; or at rest—7 patients. Two additional patients without effort angina or evidence of structural cardiac disease had severe anginal attacks due to hypoglycemia.

¶ This patient had chest pain due to (1) angina pectoris and (2) hiatal hernia.

There were 4 patients—not listed in the table—with angina plus non-anginal chest pain induced by eating and relieved by belching and due to abdominal disorders.

V. *Relation of Anginal Attacks to Certain Additional Factors*

	No. of cases	%
Attacks induced by *emotion**	14	18.2
Attacks induced by *cold*†	10	13.0
Respiratory functions:		
Breathing	1‡	1.3
Coughing	1§	1.3

* Emotion induced seizures in 6 of 8 patients with aortic lesions.

† Cold sheets (1), cold drinks (2), cold wind plus mild exertion (7).

‡ Rheumatic aortic stenosis—suspicious signs of adhesive pericarditis.

§ Congestive failure with severe attacks of coughing—pain produced by prolonged seizure only, *e. g.*, by the exertion of coughing—not the act of coughing.

VI. *Nocturnal Pain: Analysis of Precipitating Factors**

	No. of cases	%
Recumbent posture	11	14.3
Spontaneous hypoglycemia	2	2.6
Paroxysms of ectopic tachycardia	2	2.6
Nightmares	1	1.3
Cold sheets	1	1.3
Paroxysmal dyspnea	1	1.3
Unexplained	3	3.9
Total	21	27.3

* Two additional patients had nocturnal pain due to hiatal hernia.

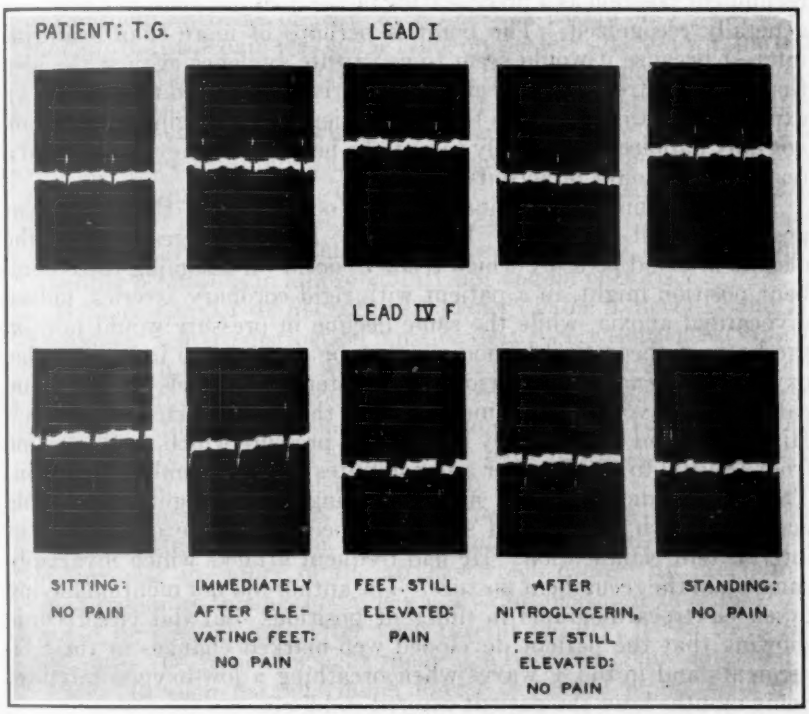


FIG. 1.—Patient T.G. The changes developing on elevation of the feet appeared slowly and hence were not the result of alterations in the electrical axis of the heart. Nitroglycerine relieved the pain and caused partial reversal of the electrocardiographic changes, which quickly returned to normal on assumption of the upright posture.

Case Studies. CASE 1. A white male, aged 55, complained of a feeling of substernal pressure radiating to the left shoulder, brought on by walking and relieved within 3 to 8 minutes by rest. He had also noted that when he would lie down the discomfort would set in within a few minutes and would become progressively worse until he assumed the sitting posture, which was followed by gradual disappearance of the pain. He insisted that the discomfort produced by lying down was identical in location and character with that caused by effort. However, the discomfort in the recumbent position tended to last longer if he remained in this posture. Sitting in a chair with the feet elevated would likewise induce a typical attack, while sitting in a chair in an upright posture did not cause pain. Nitroglycerine relieved both the pain induced by

effort and that caused by recumbency. Repeated roentgenographic studies of the stomach revealed no evidence of hiatal hernia. Electrocardiograms were made in various positions and also before and after exercise. It was found (Fig. 1) that the recumbent posture induced the same changes in the electrocardiogram which occurred on physical exertion. Even though he remained in the recumbent position the electrocardiographic changes tended to return to normal following nitroglycerine. Several months later, while walking slowly, the patient suddenly fell to the ground and expired.

This patient constituted a striking example of the *angina decubitus* of the older authors, that is, of anginal attacks occurring in the recumbent position. Even though this condition has been reported in the literature from time to time for many years, the frequency of the recumbent position as a precipitating factor does not seem to have been generally recognized. The point is perhaps of more than academic interest because it would seem to constitute evidence against the idea that the ideal treatment for angina pectoris is prolonged rest. My own experience in this matter is that the patients with angina pectoris are not only happier but actually seem to be healthier if they are allowed a reasonable amount of activity.

The mechanism of anginal attacks occurring in the recumbent posture is still unknown. Elsewhere,[13] I have suggested that the decline in blood pressure which tends to occur on assuming the recumbent position might, in a patient with rigid coronary arteries, induce myocardial anoxia, while the same decline in pressure would not, on the basis of theoretical hemodynamics, be expected to induce cardiac oxygen deficiency in a person with distensible vessels of the same caliber. In favor of such a mechanism is the case reported by Rubin.[23] His patient had an extremely labile blood pressure which would decline from 180/100 to 120/70 after a few minutes in the recumbent position. The patient did not have attacks during effort despite reasonable activity, which was limited somewhat because of the coëxistence of intermittent claudication. He had frequent attacks which invariably came on in the recumbent posture. The author did not mention having taken electrocardiograms in different positions, but did cite records showing that the patient developed well-marked changes in the S–T segments and in the T waves when breathing a low-oxygen mixture. Some months later the patient expired suddenly.

A further investigation would seem to be needed of blood pressure changes and other alterations in circulatory dynamics in patients with angina of recumbency before any definite conclusions can be drawn as to the mechanism of such attacks. The following patient is an example of an individual who had pain during effort and also during recumbency, the attacks being dependent on two different disorders.

CASE 2. A white female, aged 65, had had several attacks of "pressing" pain localized just to the left of the sternum in the precordial area, while washing dishes, and two attacks while walking up-hill. Standing or sitting quietly brought relief in a few minutes. In addition she had had numerous attacks of similar pain coming on shortly after getting into bed. Five weeks before admission to the hospital she had a severe attack of pain lasting several hours, associated with an initial rise in systolic blood pressure to 180 mm. and followed by a fall to 120 mm., her usual pressure being approximately 160.

Several days later her physician heard a friction rub over the precordium which disappeared in 48 hours, and at that time the patient had slight fever. When she was seen some weeks later the physical examination was negative except for minimal hypertension and slight cardiac enlargement. Electrocardiogram revealed inversion of the T wave in the precordial lead. Fluoroscopic examination of the stomach showed a small hiatal hernia. The pain induced by recumbency was not relieved by nitroglycerine but was benefited by atropine.

It seems likely that in this patient the pain brought on by the recumbent position was due to the hiatal hernia even though it had the same character and distribution as the pain brought on by effort and due to angina pectoris.

Inquiries as to the relative effects of the various recumbent postures in producing attacks of pain were negative except in 1 patient who thought that the pain was worse lying on the left side and was partially relieved by turning on the right. Since this patient had, in addition to typical angina pectoris, a good many of the manifestations of anxiety neurosis, a condition in which precordial pain while lying on the left side is often encountered, the significance of the difference in the two positions is questionable. In any case it can be stated that the recumbent posture is a fairly frequent precipitating cause of anginal attacks, and also that a pain which tends to be aggravated by the sitting or standing position is in all probability not angina pectoris.

B. The Effect of Muscular Effort (Table 3, parts II and III). Obviously a sharp distinction must be drawn between *general muscular exercise* such as walking, which puts no particular strain on any of the muscles in the region of the chest, and *specific muscular movements* such as bending the body, raising the arm, and so forth. It should be noted that slightly more than 90% of the patients in this group gave a definite and clear-cut history of pain induced by effort. Many of these patients had attacks which occurred under varying circumstances at rest. However, from a standpoint of diagnosis, the important feature was the story of the attacks which came with exertion. In most instances this history was readily obtained, but in a few cases it would be elicited only after very careful inquiry, for in these latter instances the patient sought medical advice for some unrelated disorder. In such patients much finesse is needed in taking a proper history in order to avoid "leading" the patient and in order to maintain in the patient's mind a clear distinction between shortness of breath and a mild pressure sensation or similar discomfort.

The patients who had pain which was not related to effort are of particular interest, for it is this group of individuals who are likely to constitute the most difficult diagnostic problems, and in whom errors are often made. These subjects will be discussed in more detail later.

In his original description of angina pectoris, Heberden[16] stressed the relationship of the pain to effort and the frequency of sudden death. Many later authors, losing sight of these cardinal features of the disease, began to apply the term "angina pectoris" to a motley array of unrelated disorders having nothing in common except the presence of discomfort in the chest. The state of confusion so engendered persisted for more than a century and was not dissipated until

the now classical work of Keefer and Resnik[18] appeared. These authors stressed Heberden's original criteria, reconciled the conflicting "aortic" and "coronary" theories and pointed out that angina pectoris was a clinical entity in the sense of the course of the disease, was a physiologic entity in the unity of the causative mechanism of the pain, but was not a pathologic entity in that the same functional disturbance—myocardial anoxia—might be induced by a variety of morbid states.

Eight individuals complained not only of pain on general exertion such as walking, but of discomfort induced by specific movements of the muscles of the shoulder or arm. This pain not only differed from that of angina in regard to the condition inducing it, but was of longer duration, different intensity, and often of different quality, being typically aching and occasionally throbbing in character. Discomfort of this type following myocardial infarction has been described by several authors,[2,4,7,8,17] and a few[2,13] have mentioned it as occurring in patients with angina pectoris who have not had myocardial infarction. Presumably, it represents the reflex effect on skeletal tissues of the cardiac disorder. This type of pain may be very confusing because there are certain patients in whom this symptom is prominent and dominates the picture, while the pain of angina may be decidedly in the background. Such a case has been reported elsewhere.[14] The pain may be identical in character with that produced by various disorders of the shoulder joint or other skeletal tissues in the absence of coronary disease. The decision as to whether or not angina pectoris is present cannot be made on the clinical features of this referred pain but must be based on the presence of the typical anginal story. Since the question of "coronary shoulder pain" will be discussed in considerable detail in a future publication dealing with chest pain arising in the skeletal tissues, the matter need not be considered further now.

C. Anginal Attacks in Relation to Various Alimentary Tract Functions. The data are summarized in Table 3, part IV. It may be noted that anginal attacks were not accompanied by discomfort on swallowing in any patient. Two subjects who had dysphagia had other disorders in addition to angina pectoris. There was likewise little relationship to expulsion of flatus or to constipation, although the act of defecation occasionally induced seizures in 3 patients. The rarity of vomiting in relation to anginal attacks is also noteworthy. There were 4 patients who had abdominal disorders which induced non-anginal pain in the chest, the pain being completely or partially relieved by belching. However, in addition to these there were 7 other patients in whom no evidence of any primary abdominal disorder could be found, but who insisted that attacks were more readily induced by effort when there was abdominal distention, who occasionally had attacks occurring at rest and induced by distention and who had obtained either partial or complete relief by belching. These findings are not surprising when one recalls the recent studies of Gilbert, LeRoy and Fenn,[11] who have shown by means of the *thermostromuhr* that constriction of the coronary arteries of the dog may be reflexly induced by distention of the stomach. The same authors[10] showed that

in each of 3 patients with angina pectoris the ingestion of food caused a decrease of 20 to 40% in the length of time required to produce anginal attacks by breathing 10% oxygen. That the effect of meals was exerted—at least partially—through a reflex mechanism, rather than solely through increased cardiac work, was suggested by the following points: (1) atropinization prevented the effect of meals; (2) some patients could relieve the attacks produced by distention either by belching or by loosening the belt. It therefore seems to be established that abdominal distention may, in certain patients, be an important trigger factor in precipitating attacks of angina pectoris.

Since the time of Heberden, it has been recognized that eating often induces anginal attacks. Much less emphasis has been placed on the fact that eating may likewise tend to prevent the seizures. In this series there were 6 patients who had anginal attacks occurring at rest shortly after meals. Five of these also had typical effort angina. The other patient gave no history of a relationship to exertion, but led an unusually sedentary life. Seventeen subjects had noted that considerably less exercise was required to induce the attacks shortly after meals than several hours later, but none of them had attacks after meals if they remained at rest. *Twelve patients had found that the ingestion of food tended to prevent the seizures.* Ten of these had the usual complaint of pain on effort and, of them, 3 had found that approximately 3 hours after meals less effort was required to induce pain than at other times. The remaining 7 patients in this group had, in addition to attacks during effort which were not related to meals, occasional seizures at rest, the resting attacks occurring almost entirely in the period of 2 to 5 hours following food.

There were 2 patients who had never had anginal attacks with effort, but who had numerous severe attacks occurring at rest, never within the first 2 hours after eating. One of these patients had been reported elsewhere[15] as an instance of angina pectoris without structural cardiac disease and dependent on glucose deficiency. The chief findings in regard to the other patient may be summarized as follows:

Case 3. A 39 year old business man had had numerous attacks of constrictive pain in the region of the cardiac apex for 5 months, accompanied by pain and numbness of the left arm. The intensity varied from mild to very severe; the total duration of the attacks was 1 to 2 hours, during which the pain would recur in short seizures of a few minutes with an interval of comfort lasting several minutes. He led an active life, but on no occasion had an attack been precipitated by muscular effort, by emotion or by eating. Most of the attacks had set in during the night or in the morning before breakfast. Although he had many seizures, he could not recall a single one which had begun within 2 hours after a meal. Following the severer seizures he had repeatedly been observed to have normal temperature and leukocyte counts. Electrocardiograms had been entirely normal when taken between attacks but records obtained during seizures had repeatedly shown changes considered typical of anterior infarction (Fig. 2). He had been studied in several hospitals and diagnoses of neurosis, coronary thrombosis, and of "coronary spasm" had been made.

Physical examination was essentially negative. Electrocardiograms were quite normal, both before and after strenuous exercise which produced no pain. Glucose tolerance curves displayed a decline from 154 (mg. "glucose"

per 100 cc.) at ½ hour to 60 at 3 hours. Fasting blood sugars varied from 100 (on a balanced diet) to 64 (on a high-carbohydrate diet). When put on a high-carbohydrate diet he had frequent mild seizures which had been absent for several days on a high-protein, low-carbohydrate diet. The administration of insulin—25 units—induced a mild seizure of pain and moderate change in the T waves.

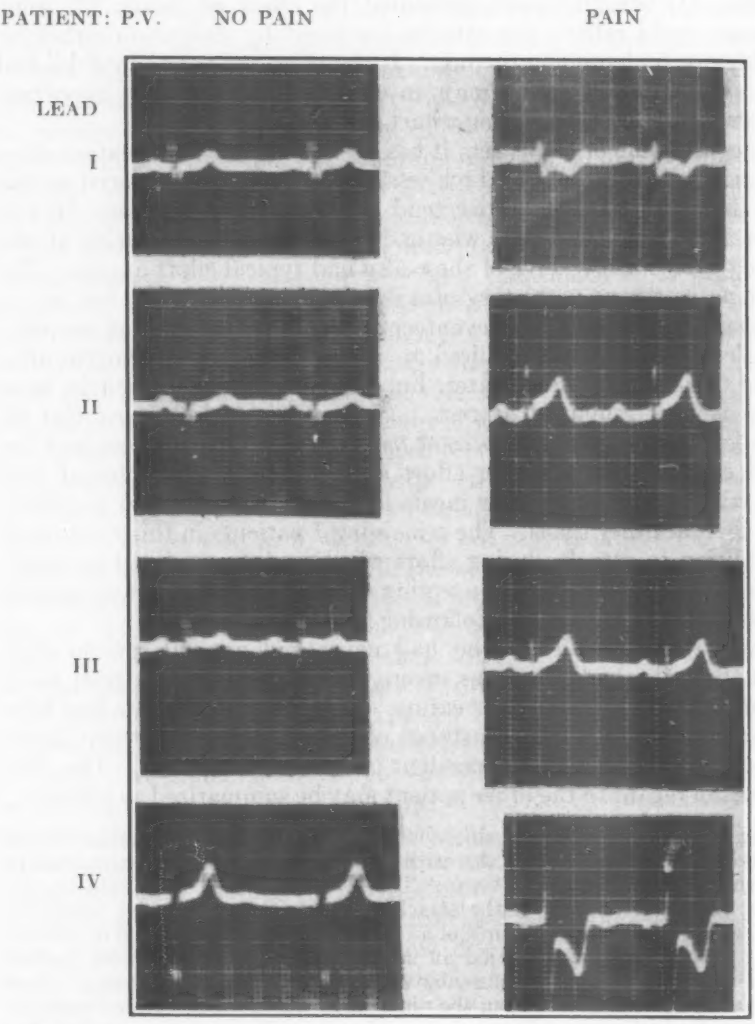


FIG. 2.—Patient P.V. The tracings on the left were taken during freedom from pain. Those on the right were obtained during an attack. The following day the record was again normal. Similar changes were repeatedly observed during an attack whether occurring spontaneously or induced by insulin.

Comment. In this patient the evidence seems reasonably complete that angina pectoris was due solely to hypoglycemia. The fact that strikingly low levels of blood sugar were not encountered does not speak against this assumption, for it has been shown[15] that symptoms due to glucose deficiency may occur in the presence of blood sugar levels within the lower limits of the normal range.

Since the relationship between glucose deficiency and anginal attacks has been discussed in some detail elsewhere[15] only a few points will be mentioned here. It has been known for more than a decade that overdosage of insulin may occasionally precipitate anginal attacks in diabetic patients with coronary sclerosis. Sippe and Bostock[24] were apparently the first writers to point out that spontaneous hypoglycemia may have a similar effect. Weinstein and Mattikow[27] recently reported 2 cases, one of whom had attacks during effort and emotion, but only provided these stimuli occurred shortly before a meal. During a glucose tolerance test this patient developed an anginal attack when the blood sugar level was 54 mg. per 100 cc., the pain being promptly relieved by glucose. The second patient was somewhat similar except attacks occurred frequently at rest as well as during exertion undertaken before meals. This individual had never had an attack except when hungry. He, likewise, developed an anginal attack during the glucose tolerance test, the blood sugar being 42 mg. per 100 cc. and relief occurring from glucose.

Patients such as Case 3, who have no evidence of structural cardiac disease* but have anginal attacks precipitated only by glucose deficiency and never by effort, must be quite rare, as I have found no other instance in the literature except for the single case previously reported.[15] However, patients who have coronary sclerosis and in whom hypoglycemia is one of several precipitating factors, are common. In this series of patients glucose deficiency, while less important than physical effort and eating, was about equal in importance to emotion as a precipitating factor. The point is of some practical importance because ordinarily the tendency toward a low blood sugar level can be readily controlled by dietary measures.

D. Emotion as a Precipitating Factor. The data are summarized in Table 3, part V. Only a little more than 10% of the patients with angina due to coronary sclerosis had attacks occurring with emotion, in the absence of exertion. However, 6 of 8 patients with disease of the aortic valve had such seizures. The tendency of patients with "aortic angina" to have attacks independently of exertion has been stressed by Lewis,[21] and the mechanism may, as suggested elsewhere,[13] be related to a greater sensitivity of normal than of diseased coronary vessels to vasomotor influences.

E. Cold as a Precipitating Factor. Since most of the patients in this series lived in areas (North Carolina and Tennessee) with relatively mild climate, the influence of cold was, as might be expected, less striking than in the cases reported by most other authors. Even so, it was noted that an occasional patient had attacks from getting into bed between cold sheets, or from the ingestion of cold drinks, while a number of individuals found that walking against the cold wind induced the attacks more readily than otherwise.

* Whether such individuals actually have minimal and "subclinical" coronary disease cannot be stated with certainty. The usual manifestations were lacking and one such patient—a young woman—has been asymptomatic for more than 6 years.

F. The Relation of Anginal Pain to Respiratory Functions. The only patient who complained that the pain was aggravated by breathing was a young woman with aortic stenosis and signs suggestive of adhesive pericarditis. The single individual who had anginal attacks with relationship to coughing, had rather severe cough as the result of congestive heart failure, and at the end of a prolonged bout of coughing would have attacks brought on by the exertion involved. The negative relationship between anginal attacks and various respiratory functions is significant in differential diagnosis, for there are a good many patients who have—in association with pleural disorders—pain with location and radiation similar to that of angina. It can be stated as a general rule, to which there are possibly a few exceptions, that any pain which bears a direct relationship to breathing, coughing, laughing, yawning or other respiratory acts, is in all probability not angina pectoris.*

G. Nocturnal Anginal Attacks. More than ¼ of the patients in this series had frequent or occasional attacks of pain occurring at rest during the night (Table 3, part VI). The most common cause of such attacks seemed to be the assumption of the recumbent posture, a factor which was shown to be important in 11 patients. Exceptionally, nocturnal attacks were found to be related to spontaneous hypoglycemia, ectopic tachycardia, nightmares, cold sheets, or the exertion associated with paroxysmal dyspnea. Finally, there were 3 patients who had fairly frequent attacks at night and in whom a relationship to any of these precipitating factors could not be found. The mechanism of their nocturnal attacks remains unexplained. In addition there were 2 patients with angina who had nocturnal recumbent chest pain believed to be not anginal in nature, as each of them had an esophageal hiatal hernia.†

IV. **Apparent Recovery from Angina Pectoris** (Table 4). The findings cannot be regarded as quantitatively accurate because one does not know how many of the patients who seem to have recovered will in the future again have anginal attacks, and one is also ignorant of the number of patients who at present are still having attacks but who will cease having them in the future. Relatively little attention has been paid to the fact that certain individuals with undoubted angina pectoris

* Aside from the 2 patients shown in Table 3, part V, there were 4 other individuals who had some of the features of angina pectoris but whose pain was related to respiratory movements. Since these subjects did not satisfactorily fill the criteria for the diagnosis of angina pectoris, they are not included in the present paper but are classified as "chest pain—cause unknown." They are being followed and thus far none of them has developed unquestionable evidence of disturbed coronary circulation.

† Since this report was written, a patient has been seen with nocturnal angina due to an additional factor—fatigue. This 67 year old male had had for 9 months attacks of "squeezing" pain just to the left of the sternum, with radiation to the left arm. The pain was induced by effort and lasted a few minutes only. He then developed typical clinical and electrocardiographic findings of "anterior" infarction. During convalescence he had several nocturnal attacks of pain, each of which occurred when he had become tired by remaining out of bed longer than usual during the preceding day. The mechanism whereby activity undertaken several hours previously induced pain is uncertain. I have observed other such cases, but since the data on this point are not complete, I am unable to state how frequently fatigue was a precipitating factor in the series of patients considered in this report.

do seem to recover. (Obviously, one cannot expect sclerotic coronary arteries to become normal. However, even though the disease in the vessels remains, the pain may cease either as the result of gradual death of the tissue from which the pain arises, or as the result of the development of collateral circulation.) As illustrations of apparent recovery the following cases may be cited.

TABLE 4.—APPARENT RECOVERY FROM ANGINA PECTORIS (ANALYSIS OF 12 CASES)*

Conditions under which recovery occurred	No. of cases	Remarks
Following coronary occlusion	4	Probable death of tissue responsible for painful stimulus
Control of hypoglycemia	2	No evidence of structural cardiac disease; disturbance of function controlled by treatment
Relief of anemia	1	
No apparent cause for recovery	5	Presumably either (1) development of collateral circulation, or (2) gradual replacement fibrosis of tissue giving rise to pain

* Recovery is assumed when no attacks have occurred for 1 year or longer, despite reasonably normal activity.

CASE 4. A 55 year old male complained in 1934 of a squeezing, precordial pain brought on by rapid walking, and relieved within a few minutes by standing quietly. Physical examination was negative. Various laboratory studies revealed mild diabetes but no changes in the electrocardiogram were noted and the heart appeared to be normal when visualized by the fluoroscope. Walking briskly up 2 flights of stairs induced a typical attack. Thirty minutes later the same exercise taken shortly after nitroglycerine caused no pain. In 1936 the attacks were somewhat more frequent, appearing 2 to 3 times a week. The following year the condition was unchanged, but after an additional year the attacks had become very infrequent, occurring only once in every 3 or 4 months. During the next 3 years the patient remained completely free of anginal attacks. The electrocardiogram was normal throughout the entire course and the amount of activity was not significantly changed.

CASE 5. A white female, aged 68, stated that 5 years before she had had severe constrictive pain in both arms, coming on with effort. After several months she had an unusually violent attack lasting several hours, requiring hypodermics and hospitalization for relief. Since then the pain had been much milder but she had continued to have slight discomfort in both shoulders when she would undertake rapid walking. The blood pressure had ranged from 180 to 200 systolic prior to the severe attack of pain, but during recent years had been much lower, varying between 120 and 140. Examination revealed slight cardiac enlargement and numerous premature beats. Electrocardiograms showed frequent ventricular premature beats and inversion of the T waves in Leads I and IV. Under observation, nitroglycerine relieved the pain and inhibited its appearance during exercise. When she was seen 2½ years later she had been completely free of pain for the preceding 18 months, even though her activities had not been significantly modified.

When anginal attacks due solely to hypoglycemia, hyperthyroidism, paroxysmal tachycardia or to severe anemia disappear following adequate treatment of the causative factor, or when the seizures vanish after myocardial infarction, the mechanism seems reasonably clear. However, it is difficult to account for the improvement which occurs gradually in the absence of such conditions, except by assuming either gradual death of the tissue, with degeneration of the nerve fibers carrying the pain impulses, or the development of adequate collateral

circulation. In any case it should be emphasized that patients may recover from angina pectoris and that such recovery is probably not very unusual.

The Occurrence of Chest Pain Due to Conditions Other Than Angina Pectoris in Patients Who Also have Chest Pain Due to Angina Pectoris (See Table 5). The two most common conditions causing non-anginal pain were myocardial infarction and reflex disorders of the skeletal tissues, probably secondary to and an indirect result of the coronary disease. Since these conditions are closely allied to angina pectoris, they need not be discussed further. Even when these disorders are omitted, there were still 15 patients, or approximately $\frac{1}{5}$ of the total number, who had two different causes of pain in the chest. The most common causes were spasticity and/or distention in the alimentary tract. The following cases are examples.

TABLE 5.—ANALYSIS OF CONDITIONS CAUSING NON-ANGINAL PAIN IN THE CHEST OR ARM IN 77 PATIENTS WITH ANGINA PECTORIS

Condition	No. of cases	%
Coronary thrombosis	35	45.4
Skeletal pain*	8	10.4
Spasticity of alimentary tract	6	7.8
Diseased gall-bladder	3	3.9
Hiatal hernia	2	2.9
Pulmonary infarction	2	2.6
Spasm of diaphragm	1	1.3
Cascade deformity of stomach	1	1.3
Total	58	75.4

* Pain in muscles, joints, or bones. In these patients the pain was probably an indirect reflex result of the disease process in the heart.

CASE 6. A 48 year old man had a substernal cramping pain radiating to the left shoulder and down the left arm as far as the elbow. This was often induced by excitement or exertion and lasted a few minutes. However, he had had numerous—*i. e.*, several score—attacks of similar pain occurring with no obvious precipitating factor and lasting from several hours to as long as 2 days. Nitroglycerine relieved the pain of short duration but had little effect during the longer seizures. Examination revealed moderate cardiac enlargement and signs of aortic stenosis. Under observation, exertion induced the discomfort, but the same exercise did not induce it when carried out immediately after nitroglycerine. Fluoroscopic examination revealed marked spasm at the lower end of the esophagus. This was not found following atropinization, which benefited markedly the attacks of long duration but did not materially effect the pain brought on by effort.

This individual's condition was very similar to that of Edeikin's[6] patient, who likewise had chest pain due to both angina pectoris and esophageal spasm. Wolferth and Edeiken[28] emphasized the frequency of esophageal spasm, pointing out that 53 cases had been observed in 2 years and that 47 of these had pain resembling in some degree the pain of angina pectoris but lacking the characteristic relationship to exertion.

A number of patients had pain in the lower left chest due to distention of the stomach or colon. Some of these were able to differentiate this from the anginal pain induced by effort; others could make no such distinction.

CASE 7. A 43 year old man had "sour stomach" and belching associated with slight substernal discomfort for approximately 15 years. For the past month he had complained of a gnawing feeling in the epigastrium, a pressure sensation in the chest, and an ache in the jaw. These several sensations were brought on by exertion and disappeared in 3 to 5 minutes with rest. The discomfort would also come shortly after meals and he thought that it was partially relieved by belching or expulsion of flatus. He was unable to differentiate between the discomfort associated with abdominal distention and that brought on by effort. Physical examination revealed minimal hypertension and slight cardiac enlargement. Roentgen ray studies of the gall bladder were negative. Gastro-intestinal Roentgen rays revealed elevation of the splenic flexure and questionable pylorospasm. Resting electrocardiogram was normal except for minimal (0.5 mm.) elevation of the S–T segment in Lead IV. Exercise induced his discomfort, and following the exertion there was a depression of 1 to 1.5 mm. in the S–T segments in Leads II, III and IV. Following inflation of the colon with air, only three-fourths as much exercise was required to bring on the same pain and the same electrocardiographic changes. Similar exertion undertaken after nitroglycerine induced no discomfort until 50% more exertion had been taken.

When, as occasionally occurs, gall-bladder disease induces pain referred to the left chest anteriorly rather than to the right side of the chest posteriorly, it may cause considerable confusion. The situation becomes doubly complex when a patient of this type likewise has angina pectoris. Such was the case in 3 patients in this series. (It seems probable that more than 3 of the 77 patients had gall-bladder disease. However, cholecystograms were not made routinely and this discussion is concerned only with the 3 patients in whom we were able to demonstrate that gall-bladder disease was causing pain in the chest in addition to pain in the chest due to angina pectoris.) An illustration of chest pain due to the two disorders is as follows:

CASE 8. A 69 year old white male was first seen in 1932 with typical anginal attacks brought on by effort and relieved by rest. In 1935 he had a severe and almost fatal myocardial infarction. Following this the anginal attacks ceased for 3 years, but in 1938 he again began having pain brought on by effort and radiating from the substernal region to the right shoulder. In addition he began to have attacks of pain in the right upper quadrant with occasional radiation to the right scapular region, but with usual radiation to the left substernal and precordial regions. This pain bore superficial resemblance to the anginal pains, but he was able to distinguish the two as regards location and duration. The pain associated with gall-bladder disease lasted for hours and was not affected by nitroglycerine. It sometimes followed eating and was often benefited by belching or vomiting. In addition, he had pain on moving the right shoulder. Roentgen rays revealed hypertrophic arthritis in the right shoulder joint in addition to stones in the gall-bladder.

In this individual we have at least 4 different painful conditions in and about the chest. These were: angina pectoris, myocardial infarction, disease of the gall-bladder, and arthritis of the right shoulder joint. Whether this arthritis was of entirely independent nature or whether the development of the arthritis was reflexly conditioned by the attacks of angina with secondary trophic changes in the joint is uncertain.

Numerous other instances could be cited of patients who had chest pain due to more than one cause. However, the other disorders which produce pain in the chest will be discussed in future publications, and the cases which have been mentioned are sufficient to justify empha-

sizing the fact that a large percentage of the individuals with angina pectoris have pain in the chest due to independent disorders. It therefore is apparent that one can readily overlook the presence of angina pectoris unless a most careful history is taken and unless the patients are studied completely, particularly as regards the observation of the response to exercise.

TABLE 6.—THE RELATIVE VALUE OF VARIOUS PROCEDURES IN THE DIAGNOSIS OF ANGINA PECTORIS

	No. of cases in which method was employed	Positive results	
		No. of cases	%
History (of pain* on effort)	77	70	90.8
Physical examination†	77	49	63.6
Electrocardiograms:			
At rest†	69	36	52.2
After effort*	10	6	60.0
Roentgenologic examination†	60	36	60.0
Exercise before and after nitroglycerine*	37	33	89.2

* The findings by these methods were often of great value in regard to the specific diagnosis of angina pectoris.

† The findings by these methods were rarely of value in regard to a diagnosis of *angina pectoris*, but were often of great value in the diagnosis of *cardiac disease*.

TABLE 7.—SUMMARY OF THE MOST IMPORTANT CLINICAL FEATURES IN THE DIAGNOSIS OF ANGINA PECTORIS

I. *Features of Positive Value**	II. *Factors of Negative Value (Their Presence Tending to Exclude Angina Pectoris)*†
1. History of relation to effort	1. Pain limited to periapical axillary or abdominal regions
2. Substernal or precordial location	2. Duration of less than 1 minute
3. Duration of 1 to 30 minutes	3. Lacinating or throbbing pain
4. Demonstration that nitroglycerine increases the amount of effort required to induce pain	4. Aggravation by breathing, coughing, swallowing, sitting or standing

* These clinical features present in 90% or more of the patients.

† These features either absent in angina pectoris, or, if present, due to associated disorders.

The Relative Value of Various Procedures in the Diagnosis of Angina Pectoris (See Tables 6 and 7). Obviously, the physical and roentgenographic examinations are of no *direct* value in diagnosis of angina pectoris. However, by furnishing evidence of cardiovascular disease in something like $\frac{2}{3}$ of the patients, these procedures are of considerable *indirect* value. The same generalization applies to electrocardiograms taken in resting subjects. Somewhat more than half of the patients displayed changes which, when considered in relation to the age and to the blood pressure of the patient, could be considered as definitely abnormal. In a majority of instances such electrocardiographic changes simply pointed toward some myocardial disorder and were not in any way characteristic of angina pectoris.

When electrocardiograms are taken following muscular effort, changes of the S–T segments and of the T waves of such a nature as to be specifically suggestive of the presence of angina pectoris may be encountered in 50 to 60% of the patients. This was true not only in the small series of my own subjects in which the procedure was carried

out, but in a much larger group of patients which has been studied by others. Thus, Twiss and Sokolow[26] have recently summarized the literature on this point and have reported observations on 66 patients with angina and 100 control subjects. Fifty-six per cent of their patients with angina pectoris developed abnormal changes in electrocardiograms, *i. e.*, changes of greater degree than were encountered in the control series. Similar findings have been reported by investigators[27,28] who have studied electrocardiographic changes induced by breathing 10% oxygen. Here again 50 to 60% of anginal patients have shown changes in the T waves and S–T segments of greater magnitude than those occurring in the control subjects.

Although, in general, the results of attempts aimed at improving the accuracy of the diagnosis of angina pectoris by taking electrocardiograms under various conditions have been disappointing, there are occasional patients with confusing histories in whom records made before and after effort may be of considerable diagnostic significance. An example follows:

CASE 9. A 71 year old female complained of precordial discomfort radiating to the right shoulder and the left arm and lasting from a few minutes to half an hour. Many of her attacks appeared when she was lying down and there would be some relief within a few minutes after sitting up. In addition, she occasionally had attacks coming on during exercise. She stated that the pain was at times aching in character and at others stabbing. She had diabetes and a non-functioning gall-bladder, as shown by cholecystograms. Electrocardiograms taken at rest were normal for a woman of her age, but following exertion there was a well marked inversion of the T waves in all leads.

Although electrocardiograms may, in certain patients, be of great value in the diagnosis of angina pectoris, too much reliance on them may be misleading. Thus, the records of one of the patients already mentioned (Case 5) in whom the attacks of angina ceased entirely, taken after she had been free from attacks for more than a year, were identical with those taken when she was having frequent seizures. Since it is the people who are having the attacks of pain rather than those who show electrocardiographic changes who are in danger of sudden death, serious errors in judgment may be made by placing too much weight on electrocardiograms in contradistinction to the clinical picture.

The methods of diagnosis thus far discussed are the objective ones. Those which rely on subjective information may now be considered. Two features which were of the greatest value in diagnosis were (1) the story of the relationship of the pain to effort which was obtained in approximately 90% of the patients, and (2) observation of the effects of exercise with and without nitroglycerine, which gave approximately an equally high percentage of positive results. Obviously these procedures often had to be carried out with the greatest of care. Some of the patients gave very confusing stories, and this was particularly true of those who had more than one cause of pain in the chest. At times history obtained initially would indicate no relationship between the pain and effort when subsequent careful questioning would point

toward such a relationship. Certain other patients were so interested in the relation of the pain to the gastro-intestinal tract, and were so convinced that "indigestion" was the source of the trouble that they had paid little attention to the effect of effort, and did not recall attacks associated with exertion until questioned in considerable detail. It was under such circumstances and also in patients with actual or impending congestive failure, who became so dyspneic with effort that they paid little attention to the coëxistent pain, that observation of the response to exercise was particularly valuable, because it served as a check against the possibility that the story of the relation to effort had been planted in the patient's mind by the physician's questions. Since pain induced by exertion occasionally occurs in conditions other than angina pectoris, the most reliable results were obtained by comparing the response to effort with that after nitroglycerine. In order to avoid the effect of suggestion, a third period of exercise undertaken following the administration of a placebo was usually employed. In emotionally unstable patients, it was often necessary to carry out this procedure a number of times before one could be satisfied with the result. However, when proper precautions were observed, the study of the effect of nitroglycerine on the exercise tolerance was found to be a valuable aid to the diagnosis of angina pectoris.

In Table 7 are summarized those clinical features which seem to be particularly helpful in diagnosis. Aside from the story and from the observation of the effect of nitroglycerine on the tolerance to exercise, the most helpful positive features were the duration of the pain and the localization in either the precordial or substernal regions. Each of these findings was present in about 90% of the patients. In addition, there were certain features which appeared to be of considerable negative value in that they occurred very rarely or not at all, or when present were due to associated disorders. These features, which occur so rarely in patients with angina pectoris as to constitute evidence against the disorder, are: (1) pain limited to the periapical, axillary, or abdominal regions; (2) duration of the pain of only a few seconds; (3) a throbbing or lancinating character of the pain; and (4) discomfort which was aggravated by swallowing, breathing, coughing or the sitting or standing posture.

There are certain findings which are ordinarily stressed in the diagnosis of angina pectoris and which occurred in about half of our patients, but which appeared in this series less frequently than in some of the other reports in the literature, and which therefore would seem to be of less diagnostic value than is generally believed (Table 8). These included (1) pain limited to the substernal region, (2) pain of constrictive quality, and (3) electrocardiographic changes either at rest or after exercise. On the other hand, there were certain features which, although less common than the ones just mentioned, still were more common in this series than one would think, from the writings on angina pectoris in the literature. These included pain of mild character, discomfort occurring at night or aggravated by the recumbent position, and distress which tended to be benefited by eating. It is

believed that the factors of recumbency and of hypoglycemia should be added to the classic list of exertion, eating, emotion and cold as important precipitating causes of the attacks (Table 8).

TABLE 8.—SOME COMMON MISCONCEPTIONS IN REGARD TO ANGINA PECTORIS

I. *Features Which Are Less Common Than Usually Believed**	II. *Features Which Are More Common Than Usually Believed†*
1. Location in substernal region or in arms	1. Mildness of pain
2. Constrictive quality of pain	2. Aggravation by recumbent posture
3. Abnormal electrocardiograms at rest	3. Beneficial effect of eating
4. Abnormal degree of change in S–T segments or T waves after effort	4. Nocturnal attacks
	5. Frequency of chest pain due to other diseases in patients who also have chest pain due to angina pectoris

* These features present in 40 to 60% of the patients.
† These features present in 15 to 50% of the patients.

Palpitation in Relation to Angina Pectoris. The data in our study on this point are not summarized because they are not complete, as all of the patients were not questioned in detail about this symptom. My general impression is that palpitation is an exceptional symptom during anginal attacks, and that its occurrence should immediately lead to the suspicion that the pain complained of is due to some other cause such as cardiac neurosis. However, there are certain conditions under which palpitation commonly occurs during anginal seizures. The most common cause is frequent premature beats. Rarely anginal attacks are precipitated by ectopic tachycardia, either auricular fibrillation or paroxysmal tachycardia. Such a patient may have pain only during the seizures. The following case is illustrative:

CASE 10. A 58 year old man was seen because of palpitation. He gave a typical story of auricular tachycardia, the attacks having been present for approximately 30 years. During the seizures he had severe palpitation, weakness, and marked apprehension, but had never had pain. Opportunity to confirm the diagnosis by electrocardiogram did not occur, but on two occasions the attacks were stopped by pressure on the eyeballs, and in all respects the seizures were typical of paroxysmal auricular tachycardia. Three years later, at the age of 61, he began to have precordial and substernal constrictive pain during the seizures. Following one rather prolonged attack he developed cerebral embolism with hemiplegia. Several years later he began to have occasional attacks of angina on walking and now, for the first time, had pain independent of the attacks of tachycardia. He expired suddenly at the age of 67, while in his usual health.

Aside from disturbances of cardiac rhythm, palpitation may occur in anginal attacks brought about by hypoglycemia. This symptom was present in 1 of the 2 patients in this series in whom hypoglycemia was the sole cause of the attacks and occurred in 8 of the 12 patients who had anginal seizures due to hypoglycemia in addition to attacks occurring with effort. The palpitation was usually absent in the seizures brought on by exertion and present in the attacks occurring at rest, due to glucose deficiency.

Thyrotoxicosis may lead to anginal attacks accompanied by palpitation, and a rarer cause is a condition which is not illustrated in this series, namely, paraganglioma of the adrenal glands with intermittent

hyperepinephrinemia. However, as a general rule, it may be said that when a patient with undoubted anginal attacks has palpitation during the seizures in the absence of a well-marked disturbance of the rate or of the rhythm of the heart, one should suspect hypoglycemia as the cause, and particularly so if the attacks occur in the resting state.

Anginal Attacks Occurring Independently of Muscular Effort. *Individuals Who Had Never Had Pain in Relationship to Exertion.* There were only 7 such subjects out of the 77 patients in the series. One of these individuals was almost bedridden because of thrombo-angiitis obliterans. Two other subjects in the group led unusually sedentary lives and indulged in practically no exercise other than walking a few yards at a time. One patient had paroxysmal auricular fibrillation and another had paroxysmal tachycardia. The pain in these 2 subjects appeared only during the seizures of ectopic rhythm, but neither of them engaged in much exercise. The remaining 2 patients led active lives and were subjected to strenuous exercise under observation, but had no pain. These 2 subjects had angina only when hypoglycemia was present. One of them has been reported in a previous publication[15] and the other is described as Case 3 in this communication. It thus appears that when a patient is suspected of having angina pectoris and yet gives no story of any relationship of the seizures to physical exertion, one should suspect ectopic tachycardia, glucose deficiency, or that the individual is leading an unusually restricted life. Most of the subjects who fall into the latter group can be induced to have an attack if sufficient physical effort is undertaken. However, in the case of individuals with ectopic tachycardia and with hypoglycemia, anginal attacks may occur in spite of the fact that the same individuals under different circumstances may undertake severe exertion and remain entirely free of pain.

Individuals With Frequent or Occasional Angina of Effort and With Frequent Attacks Occurring in the Absence of Effort. Such patients include a fairly large percentage of all individuals with angina pectoris, and since cases of this type are the ones which are likely to offer the greatest difficulty in diagnosis, it may be worth while to re-summarize the factors which may induce attacks at rest.

The importance of the recumbent posture has been stressed. Most patients who have attacks during recumbency have seizures readily provoked by mild exercise. However, occasionally a patient may have relative freedom from attacks during effort and yet have fairly frequent seizures coming on while lying down. In such a patient, unless a clear-cut story can be obtained of attacks during exertion, it may be necessary to have the patient undertake exercise under observation in order to establish a diagnosis.

There are a good many patients who have occasional attacks during effort and who have seizures occurring at rest without any obvious precipitating factor, in whom careful analysis will demonstrate that the attacks coming on at rest are due to glucose deficiency. The following patient is an example:

CASE 11. A 44 year old, very obese white male had, while walking at a rapid rate against the wind in very cold weather, an attack of discomfort consisting of a dull heavy sensation over the entire anterior chest. This pain lasted for about 30 minutes. Several months later he had a series of similar attacks, lasting 1 to 2 hours, occurring at rest, the last of the series being more severe, enduring for about 8 hours, and being associated with the typical manifestations of myocardial infarction. Since that time he had had numerous short seizures of similar but milder pain occurring without any relationship to effort, but his activities had been markedly restricted. These attacks had usually come 3 to 5 hours after the preceding meal. For several years he had noted weakness, nervousness and tremor prior to taking food, the symptoms being promptly relieved by eating. The only important finding on physical examination was marked obesity. Blood pressure was 120/84. Fluoroscopic examination revealed suggestive hypertrophy of the left ventricle. Electrocardiograms displayed moderate downward displacement of the S–T segment in Lead II, slight displacement in Lead III, and a diphasic T 4. Following the ingestion of glucose his blood sugar was 220 mg. per 100 cc. after 1 hour and 50 mg. per 100 cc. in 4 hours. Further inquiry revealed that in recent weeks the patient's usual attacks of weakness and nervousness, which had occurred several hours after meals for years, and were relieved by eating, had been associated with the pain in the chest.

The importance of large meals and of emotional disturbances in causing anginal attacks at rest has already been stressed, and the occasional patient in whom attacks occur as the result of abdominal distention independently of meals has been mentioned. It should be emphasized that patients with angina due to diseases of the aortic valve are considerably more prone to attacks at rest than are patients with angina as the result of coronary sclerosis.

An occasional individual will have anginal attacks occurring during the night and brought about by unpleasant dreams. There was only one such case in the present series. She also had attacks with exertion, but these were less common than those associated with nightmares.

As patients develop either congestive failure or intermittent claudication, seizures previously appearing with effort may disappear because the subject is no longer able to undertake as much muscular effort as previously. After a time such individuals may begin to have attacks at rest. This occurred in one patient in this series and may have taken place in another.

When the several precipitating factors which have been mentioned have been excluded, there still remain certain patients who have attacks at rest in the absence of any known cause. Possibly in such individuals measurements of blood pressure and other circulatory functions might yield information concerning the mysterious mechanisms concerned in the seizures.

Individuals With Attacks of Angina at Rest as a Prelude to Myocardial Infarction. The conditions which have thus far been mentioned as causes of angina without exertion usually lead to only occasional attacks. When a patient begins to have frequent attacks at rest, and particularly if the attacks are unusually severe and last for an hour or more, the chances are strong that the patient will soon develop a myocardial infarction. In a fairly large percentage of cases the onset of infarction is preceded by such a sequence of events. Occasionally,

such patients with *status anginosus* may die suddenly without having ever developed the infarction. It is probable that these "pre-infarction" seizures are the most common cause of resting angina, particularly if the attacks are severe. However, this type of angina has not been considered in the present publication because it is closely allied to myocardial infarction and may be more properly considered in a future report dealing with that disorder.

It must be granted that many patients with typical angina pectoris have occasional attacks at rest, and that in exceptional circumstances all of the attacks in a given individual may occur in the resting state. However, the recognition of this fact should not lead the physician into a state of being ready to diagnose angina in the absence of the story of muscular effort. Pain simulating angina pectoris in location and in character, but without a relationship to effort, is of common occurrence, and in the majority of instances the pain is not really that of angina pectoris at all but is dependent on a disorder of organs other than the heart. One should therefore demand rather conclusive evidence before being willing to place the ominous label of angina pectoris on a patient who does not have attacks with exertion. This fearful disease may be simulated by many others. The differentiation, while often difficult, is usually possible, and it is primarily with the problem of such differentiation that future reports in this series will deal.

Summary. An analysis of 77 patients with angina pectoris has been made, with particular reference to the characteristics of the pain and its relationship to various body functions.

The pain was felt in the substernal *location* in only about ½ the patients. Pain entirely limited to the periapical, axillary or abdominal regions did not occur in any case.

The *duration* of the pain was usually a few minutes only, rarely longer than ½ hour. No patient had pain lasting for a few seconds only.

Pain of great *intensity* was exceptional, the discomfort being mild or minimal in more than ½ the patients.

The discomfort was constrictive or heavy in *character* in only about 50% of the cases. Frequently, the pain was of an aching quality; burning discomfort was occasionally found; while lancinating pain was encountered in only one subject.

In addition to the generally recognized "trigger" factors of exertion, eating, emotion and cold, the recumbent posture and glucose deficiency were found to be common precipitating causes of the seizures. In exceptional patients, anginal attacks with typical electrocardiographic changes may be induced by spontaneous hypoglycemia in patients who have no seizures with severe effort and no evidence of structural cardiac disease. The act of eating may precipitate anginal attacks in certain patients and may prevent the attacks in other subjects.

Pain induced by the sitting or standing position or aggravated by breathing, coughing or swallowing can usually be safely ascribed to disorders other than angina pectoris.

In the diagnosis of angina pectoris the most important features are: (1) the history of relationship to effort, (2) the short duration of the pain, (3) the demonstration that the amount of muscular effort required to induce the pain is increased by nitroglycerine.

A large percentage of patients with angina pectoris also suffer from chest pain due to other disorders. Such disorders may either be related to angina pectoris (as in the case of myocardial infarction and reflex disturbances of the skeletal system) or unrelated to it (as in the case of gall-bladder disease, hiatal hernia, esophageal spasm, and so forth). Because of the frequent coëxistence of two causes of chest pain, one of them may be overlooked unless unusual care is employed in obtaining the history.

Occasional patients—about 10% in this series—may have anginal attacks which have never been related to effort. Among the causes of such attacks are status anginosus ("coronary insufficiency," "pre-infarction angina") ectopic tachycardia, spontaneous hypoglycemia, and conditions such as intermittent claudication, congestive failure and undue anxiety about the cardiac condition, which induce the patient to lead an unusually sedentary life. It is in this group of patients that the greatest diagnostic difficulty is likely to be encountered.

REFERENCES

1. Ashkenaz, D. M.: Am. J. Physiol., **120**, 587, 1937.
2. Askey, J. M.: Am. Heart J., **22**, 1, 1941.
3. Barnes, A. R., and Pruett, R. D.: J. Michigan Med. Soc., **41**, 943, 1942.
4. Boaz, E. P., and Levy, H.: Am. Heart J., **14**, 540, 1937.
5. Davis, L., Pollock, L. J., and Stone, T. T.: Surg., Gynec. and Obst., **55**, 418, 1932.
6. Edeikin, J.: J. Am. Med. Assn., **112**, 2273, 1939.
7. Edeikin, J., and Wolferth, C. C.: Am. J. Med. Sci., **191**, 201, 1936.
8. Ernstene, A. C., and Kinell, J.: Arch. Int. Med., **66**, 800, 1940.
9. Evans, C., and Bourne, G.: Brit. Heart J., **3**, 69, 1941.
10. Gilbert, N. C., Fenn, G. K., and LeRoy, G. V.: J. Am. Med. Assn., **115**, 1962, 1940.
11. Gilbert, N. C., LeRoy, G. V., and Fenn, G. K.: Am. Heart J., **20**, 519, 1940.
12. Goodrich, B. E., and Keyes, J. W.: J. Michigan Med. Soc., **41**, 570, 1942.
13. Harrison, T. R.: Failure of the Circulation, 2d ed., Baltimore, Williams & Wilkins, 1938.
14. Harrison, T. R.: J. Am. Med. Assn., **120**, 519, 1942.
15. Harrison, T. R., and Finks, R. M.: Am. Heart J., **26**, 147, 1943.
16. Heberden, W.: Failure of the Circulation, 2d ed., Baltimore, Williams & Wilkins, p. 59, 1938.
17. Howard, T.: Med. J. and Rec., **131**, 364, 1930.
18. Keefer, C. S., and Resnik, W. H.: Arch. Int. Med., **41**, 769, 1928.
19. Levy, R. L., Bruenn, H. G., and Russell, N. G., Jr.: Am. J. Med. Sci., **197**, 241, 1939.
20. Lewis, Sir Thomas: Pain, New York, The Macmillan Company, 1942.
21. Lewis, Sir Thomas: Diseases of the Heart, New York, The Macmillan Company, 1933.
22. Miller, H. R.: New York State J. Med., **41**, 345, 1941.
23. Rubin, B.: J. Med. Soc. New Jersey, **39**, 529, 1942.
24. Sippe, C., and Bostock, J.: Med. J. Australia, **1**, 207, 1933.
25. Spillane, J. D., and White, P. D.: Brit. Heart J., **2**, 123, 1940.
26. Twiss, A., and Sokol, M.: Am. Heart J., **23**, 498, 1942.
27. Weinstein, J., and Mattikow, B.: Ann. Int. Med., **12**, 1886, 1939.
28. Wolferth, C. C., and Edeikin, J.: Penna. Med. J., **45**, 579, 1942.

INFARCTION OF THE LATERAL WALL OF THE LEFT VENTRICLE

PATHOLOGIC AND ELECTROCARDIOGRAPHIC STUDY

BY HUGO WARNEFORD THOMSON, M.D.*
BUENOS AIRES, ARGENTINA
AND
HAROLD FEIL, M.D.
CLEVELAND, OHIO

(From the Department of Medicine of Western Reserve University and the University Hospitals of Cleveland)

THE electrocardiographic (ECG) pattern of infarction of the lateral wall of the left ventricle (mid-ventricular infarction) was first described by Wood, Wolferth and Bellet.[14] They described the following ECG changes as typical: (1) Depression of the RST segment in Lead IV. (2) Depression of the RST segment in Leads I and II. This they stated was commonly, though not universally, present. (3) Absence of characteristic abnormalities in Lead III. (4) High incidence of auricular fibrillation.

The resemblance to digitalis effect in the S-T segment was also noted. One typical, uncomplicated autopsy case was reported. Left circumflex artery thrombosis was usually found to be responsible for the infarction.

Since their paper in 1938, the only report has been that of Johnston, Rosenbaum and Wilson[6] who write that "Antero-lateral infarction gives rise to characteristic changes in leads from the left side of the precordium and in Lead I. Postero-lateral infarcts often produce abnormally large Q waves in the leads from the extreme left side of the precordium and give rise to inverted T waves in Lead I and prominent Q waves in Leads II and III. When antero-septal infarction is followed by postero-lateral infarction, there is a tendency for the QRS changes produced by the former to disappear or become less typical. Under these circumstances R waves may reappear in leads from the right side of the precordium and typical or semicharacteristic modifications of the ventricular complexes of the fifth and sixth precordial leads appear for the first time."

With the object of inquiring further into the incidence and diagnostic criteria of this type of infarction, 106 postmortem cases of myocardial infarction were reviewed. The entire group of cases (Table 1) was subdivided, depending on the location of the infarct.

TABLE 1.—POSTMORTEM CASES OF MYOCARDIAL INFARCTION SUBDIVIDED ACCORDING TO LOCATION OF INFARCT

Location	No.	%
Left lateral wall	19	17.9
Right lateral wall	1	0.9
Posterior and basal	26	25.5
Anterior and apical	56	54.9

We have also added 1 case of contusion of the lateral wall of the left ventricle by a bullet wound, making a total of 107 cases. This

* Commonwealth Fund Fellow.

incidence of left lateral infarction is in accord with that of Barnes,[1] who found 8 cases in 49 cases of myocardial infarction (16.3%).

Barnes[1] in 1932 stated that in a heart with an unusually large left circumflex artery or with neighboring arteries congenitally small or obstructed by disease, occlusion of this vessel results in a more extensive infarction, involving the anterior or posterior wall of the left ventricle, producing complex electrocardiographic patterns.

We have divided our cases of lateral infarction into the following groups: (1) Recent pure lateral infarcts with "typical" electrocardiograms (4 cases). (2) Recent pure lateral infarcts with atypical electrocardiograms (5 cases). (3) Recent lateral infarcts combined with infarction of some other part of the myocardium (3 cases). (4) Remote lateral infarcts (7 cases).

In every case a postmortem examination was performed and an ECG had been taken just before death in the cases of recent infarction. The location of the recent infarcts in the first 9 cases are illustrated in Figure 1, together with the coronary arteries involved. Figure 2 shows the typical ECG findings in the first 4 cases. Figure 3 comprises the ECG of the atypical cases.

Group I. Cases With "Typical" ECG. This group comprises those cases of recent infarction of the lateral wall which showed ECG changes similar to those described as typical of this type of infarction by Wood, Wolferth and Bellet.[14] These patients had not received digitalis at the time the ECG showing the typical changes were taken. Of these cases, 3 had remote infarcts in addition to the recent infarction. In 1 case the infarct was extensive and occupied a part of the anterior wall; in another the infarct extended slightly into the posterior wall. The left circumflex coronary artery was occluded by a recent thrombosis in 1 case; in 2 cases the left coronary artery was thrombosed near its origin; in another case only sclerosis of these arteries was present.

In all of our 4 cases, the S-T segment was depressed in the chest leads. These cases showed a slight depression of the S-T segment in the limb leads. Two of these cases showed a slight elevation of the S-T segment in Lead I. In only 1 case were the T waves upright in all leads. Contrary to the findings of Wood, Wolferth and Bellet,[14] the QRS complex showed some notching in 2 of our cases.

Case Studies. CASE 1. Female, aged 61. *Clinical Diagnosis.* Myocardial infarction; generalized arteriosclerosis. Five years previously, patient was awakened from sleep by a dull aching pain in the left chest radiating to the left shoulder and arm. Known high blood pressure for 10 years. Twenty-four hours before admission, sudden seizure of pain beginning over the precordium, radiating to the left shoulder and down to the fingers. Not relieved by nitroglycerin. This persisted until 4 hours before admission when it suddenly increased.

Physical Findings. Cyanosis, distention of neck veins, shallow respiration, slight accentuation of A_2, blowing systolic murmur at apex was noted. A few coarse râles over both bases; later, loud moist râles. White blood cell count 10,000; sedimentation rate 0.5 mm. per minute. Temperature rose to 39.2° C. on the 2nd hospital day. On 5th hospital day there was a sudden return of agonizing pain. Cheyne-Stokes respiration, diaphoresis, cyanosis and a fall

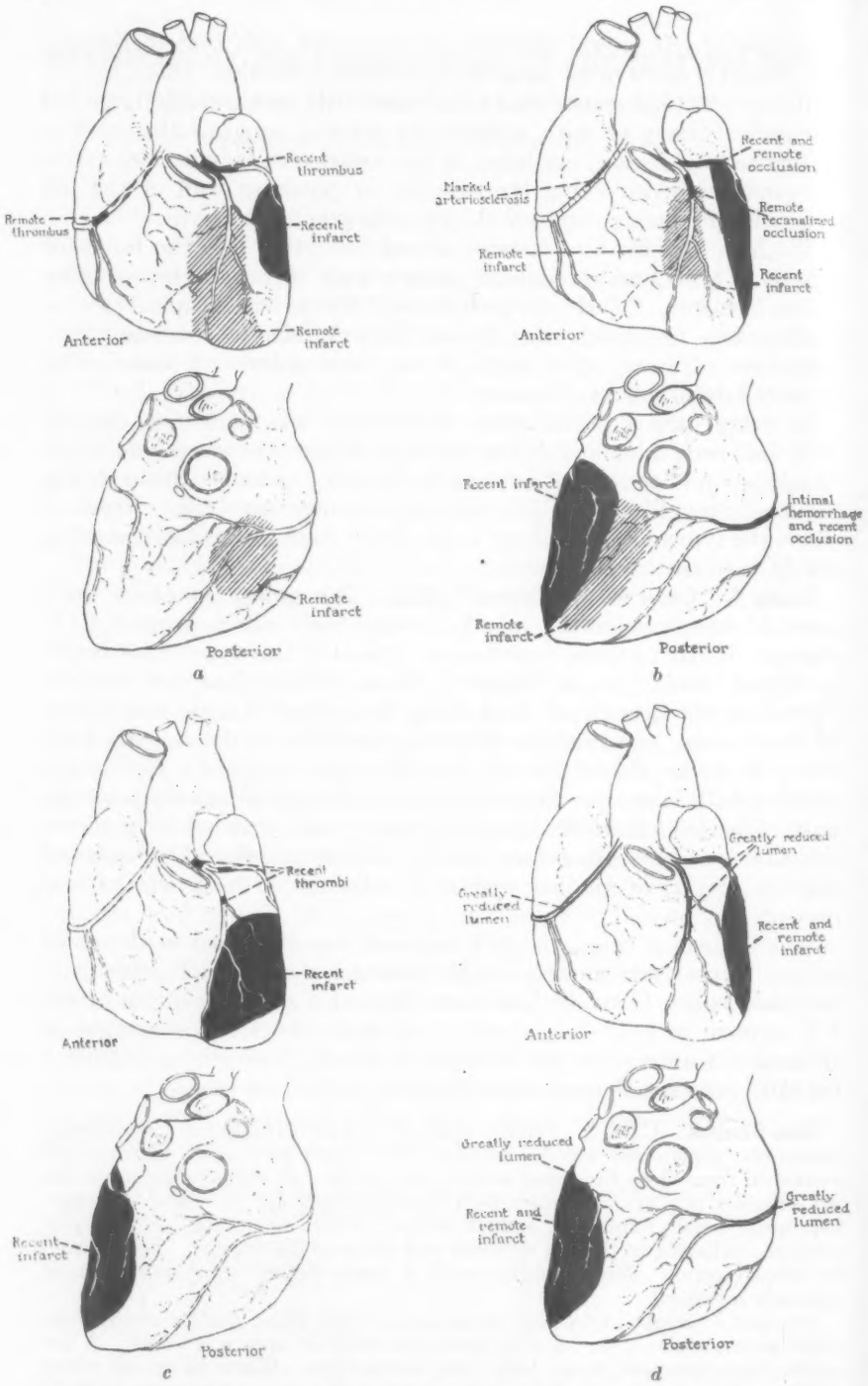


FIG. 1 (*a–i*).—Diagrams of hearts, showing the location of recent pure infarcts of the lateral wall of the left ventricle and the vessels occluded by thrombi, or the lumina reduced by atherosclerosis.

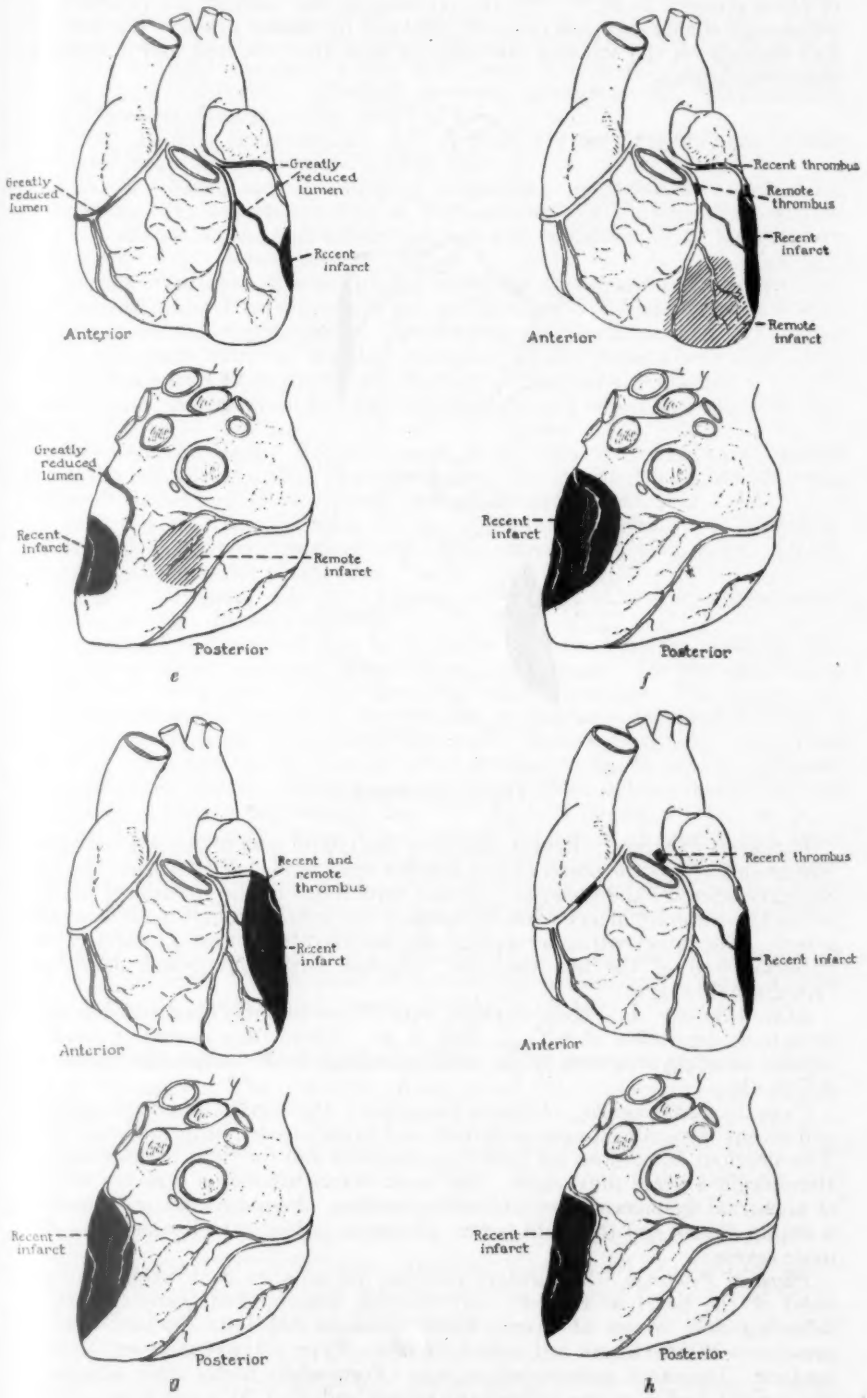


FIG. 1.—*(Continued.)*

of blood pressure to 90/70. On the 7th hospital day another severe attack of pulmonary edema and pain occurred, followed by sudden death. The patient had digitalis on the 4th and 5th hospital days after the first and diagnostic electrocardiogram.

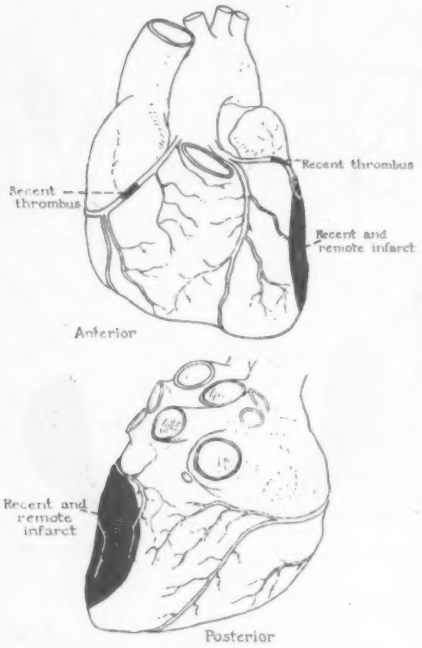


FIG. 1.—(*Continued.*)

Pathologic Findings. Recent infarct of the lateral wall of the left ventricle. Remote infarcts of the posterior and anterior walls of the left ventricle. Marked coronary sclerosis and stenosis. Recent thrombosis of the circumflex branch of the left coronary artery with extension of thrombus into left main coronary artery. The interventricular septum was involved by a remote infarct of the posterior wall of the left ventricle. Cardiac hypertrophy and dilatation (400 gm.) (Fig. 1, *a*).

ECG, 1/30/40: A-V nodal rhythm, rate 75 per minute; abnormal left axis deviation; depression of $S\text{-}T_{1,2,4R}$ (Fig. 2, *a*). 2/5/40 (day preceding death): regular sinus rhythm, rate 98 per minute; voltage lower; stepladder ascent of S-T in 4R.

CASE 2. Male, age 57. *Clinical Diagnosis.* Myocardial infarction, remote and recent; generalized arteriosclerosis and hypertension; bronchopneumonia. Two previous admissions for bronchopneumonia and for right herniorrhaphy. Hemiplegia 3 years previously. One week before admission a severe attack of nocturnal dyspnea with substernal oppression. Four days before admission a similar attack and the night before admission a third attack which was still more severe.

Physical Findings. Respiratory distress, diffuse apex beat, slight enlargement of the heart to the left, soft blowing, high-pitched systolic murmur following first sound at apex. Blood pressure 150/110; elevated venous pressure. White blood cell count 10,000. Type 23 pneumococci in the sputum. Increased sedimentation rate. Forty-eight hours after admission the patient had a severe pulmonary edema and died 36 hours later. ECG was taken on day of admission previous to digitalization.

Pathologic Findings. Recent infarct of the lateral wall of the left ventricle. Remote infarct of the anterior and posterior wall of the left ventricle. Complete occlusion of the left circumflex coronary artery by a recent thrombus. Stenosis of right coronary artery with some intramural hemorrhage and lymphocytic infiltration. Marked coronary arteriosclerosis. Hypertrophy and dilatation (500 gm.) (Fig. 1, *b*).

ECG: Regular sinus rhythm, rate of heart 114 per minute; right bundle branch block; depression of $S\text{-}T_{4R}$ (Fig. 2, *b*).

CASE 3. Male, age 78. *Clinical Diagnosis.* Parkinsonism; myocardial infarction. He had encephalitis in 1920 followed by Parkinsonism; angina for 3 weeks and a constant substernal pain with weakness for 12 hours before admission.

Physical Findings. Severe distress, peripheral cyanosis and cold extremities, a few basal râles. Heart normal in size and in sounds. Blood pressure 130/110. White blood cell count 14,500. Accelerated sedimentation rate. The day after admission auricular fibrillation began and the patient was digitalized. He suddenly expired on the 6th hospital day. The first and diagnostic electrocardiogram was taken on the day of admission and before digitalis had been given.

Pathologic Findings. Recent infarct of the left ventricle, most marked over the left lateral wall. The infarction of the left ventricle anteriorly was subendocardial and did not extend through the epicardium (Fig. 1, *c*).

ECG, 1/4/43: Regular sinus rhythm, rate 115 per minute. T_1 negative, $S\text{-}T_{2,3,CR2,4R}$ depressed; frequent ventricular extrasystoles (Fig. 2, *c*). 1/7/43: Paroxysmal auricular fibrillation.

CASE 4. Female, age 69. *Clinical Diagnosis.* Coronary thrombosis; arteriosclerosis; diabetes mellitus.

Complaint of precordial pain for 2 years. Persistent pain in chest and left arm for 2 weeks. Known hypertension for 8 years. On the day before admission, the patient became irrational, then comatose. The sputum for the last 3 days was grossly bloody and she vomited large amounts of blood.

Physical Findings. Ashen cyanosis, coma, shallow breathing, moist râles in both bases, systolic murmur to left of sternum in fourth intercostal space. Protodiastolic gallop. White blood cell count 8950; sedimentation rate not increased. Died in 1st hospital day. No digitalis therapy.

Pathologic Findings. Recent and remote infarction of lateral and basal wall of left ventricle. Coarse fibrous scar in interventricular septum. Fibrous obliteration of pericardial cavity. Severe coronary arteriosclerosis and stenosis. Lumen of left circumflex coronary artery greatly reduced. Hypertrophy and dilatation of heart (425 gm.) (Fig. 1, *d*).

ECG: A slight elevation of S-T segment in Lead I with the T wave inverted in the same lead. In both chest leads there was an abnormal depression of the S–T segments, proportionally greater in 4R (Fig. 2, *d*).

Group II. Cases With Atypical ECG. This group comprises Cases 5 to 9 inclusive. The infarcts all involved the mid-ventricular region of the left ventricle. In 3 cases the left circumflex artery was obliterated by recent thrombosis; in 1 case the left coronary artery was occluded by a thrombus at its origin; in 1 case only sclerosis was present in the coronary arteries. In 2 cases there was occlusion of one of the other coronary arteries. Wood, Wolferth and Bellet,[14] in discussing their atypical cases, observed that the ECG could be modified by the extension of the infarct into the anterior or posterior walls, so producing the atypical ECG findings. Two of our cases showed changes corresponding to a recent posterior and basal infarct and 1 case suggested an old posterior and basal infarct. In the other 2 cases, fibrillation was present but 1 of these had a depression of the S-T

segment in the chest lead which might have been more pronounced if pericarditis had not been present.

Case 5. Female, age 68. *Clinical Diagnosis.* Arteriosclerosis; hypertension; coronary occlusion; cerebral hemorrhage and multiple infarction of the brain. Two previous admissions, the one for a surgical condition and the other for hypertensive heart disease and cardiac failure. The patient returned to the Out-patient Department after 1 month, complaining of pain and shortness of breath. On the same evening she became stuporous and developed left hemiplegia.

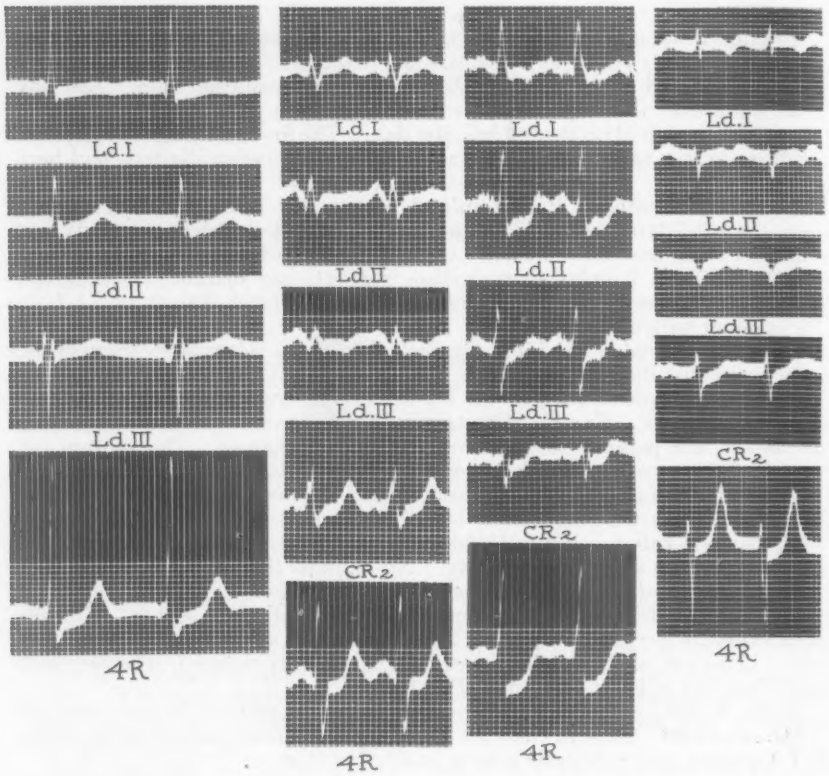


Fig. 2 (*a–d*).—Electrocardiograms of patients with pure lateral infarcts, with "typical" changes.

Physical Findings. Stupor, left hemiplegia, moderate venous distention, crepitant râles in the left base, enlarged heart, harsh systolic murmur at the apex, pulsus alternans, enlarged liver. White blood cell count 9450; increased sedimentation rate. She received digitalis during her hospital stay but the ECG was taken the day before admission when she had been digitalis-free for 1 month. On the 4th hospital day the patient became comatose and expired on the 5th hospital day.

Pathologic Findings. Recent infarct of the lateral and posterior wall 3 cm. from apex of left ventricle. Severe sclerosis and stenosis of left descending and left circumflex coronary arteries. Remote infarct of the posterior wall of the right ventricle. Cardiac hypertrophy and dilatation (625 gm.) (Fig. 1, *e*).

ECG: Left axis deviation. There was some elevation of the S-T segment in Leads II, III and 4R (Fig. 3, *a*).

CASE 6. Male, age 55. *Clinical Diagnosis.* Coronary occlusion and multiple pulmonary emboli. Patient had attack of "acute indigestion" immediately following lunch on the day of admission. Severe substernal pain radiating into both arms followed by acute dyspnea and orthopnea.

Physical Findings. Râles in both bases of the lungs, enlargement of heart. Increased sedimentation rate; white blood cell count 13,050. The patient was digitalized. No digitalis had been given previous to the ECG.

Pathologic Findings. Recent infarct of lateral, posterior and basal portions of left ventricle. Remote infarct of anterior and apical portion of left ventricle and interventricular septum. Recent thrombosis of left circumflex coronary artery. Remote thrombosis of descending branch of left coronary artery. Marked coronary arteriosclerosis. Focal acute fibrinous pericarditis. Hypertrophy and dilatation of heart (520 gm.) (Fig. 1, *f*).

ECG: Typical picture of posterior and basal infarction; auricular fibrillation (Fig. 3, *b*).

CASE 7.—Female, age 85. *Clinical Diagnosis.* Recent coronary thrombosis; arteriosclerosis. Right hemiplegia 1 year before entrance. Increasing shortness of breath, orthopnea and cough for 1 year. One month previous to admission an attack of severe substernal pain lasting for about 1 week. This again occurred 1 day before admission and was followed by several attacks of vomiting.

Physical Findings. Mild dyspnea, râles in both lung bases, slight enlargement of heart to the left. Blood pressure 130/80. White blood cell count 9700 on admission; on 9th hospital day it was 13,000. Increased sedimentation rate. Patient was treated with nicotinic acid and digitalis without any response. She became comatose, had Cheyne-Stokes respiration and died on the 17th hospital day.

Pathologic Findings. Recent infarct of the lateral wall of the left ventricle with perforating aneurysm. Several small areas of fibrosis in the interventricular septum. Recent and remote occlusion of the left circumflex coronary artery for a distance of 5 cm. with a fresh thrombus in mid-portion. Sclerosis of coronary arteries. Pericardial adhesions. Hypertrophy and dilatation of heart (550 gm.) (Fig. 1, *g*).

ECG: Regular sinus rhythm (transient auricular fibrillation), and elevation of $R\text{-}T_{1,2,3}$ and inversion of T_{aR} (Fig. 3, *c*).

CASE 8.—Male, age 64. *Clinical Diagnosis.* Myocardial infarction, recent and remote; cardiac insufficiency; embolism of bifurcation of aorta; infarction of kidney. Two and a half weeks before admission, the patient developed an upper respiratory infection. Suddenly he became short of breath, did not respond to treatment and was hospitalized.

Physical Findings. Orthopnea, cyanosis, impaired resonance at bases of both lungs, decreased intensity of the breath sounds, many coarse and fine râles, enlarged heart, marked sclerosis of peripheral arteries. The liver was 4 cm. below the costal margin and was tender. Some ankle edema. White blood cell count 16,800. Shortly after admission the patient was digitalized. The diagnosis of saddle embolus was made and an embolectomy was done successfully. Patient died suddenly the following morning.

Pathologic Findings. Recent infarct of mid-lateral and posterior portion of left ventricle. Area of dense fibrosis in interventricular septum. Origin of left descending coronary artery occluded by recent thrombus. Right coronary artery occluded 2 cm. from origin by old occlusion. Coronary arteriosclerosis. Hypertrophy and dilatation of heart (510 gm.) (Fig. 1, *h*).

ECG: Auricular flutter and the S-T segment was deformed by P waves (Fig. 3, *d*).

CASE 9. Male, age 40. *Clinical Diagnosis.* Recent myocardial infarction; remote myocardial infarction; hypertensive cardiovascular disease. A diagnosis of coronary thrombosis with infarction of the posterior and basal portions of the heart was made 3 years before admission. Highest blood pressure was

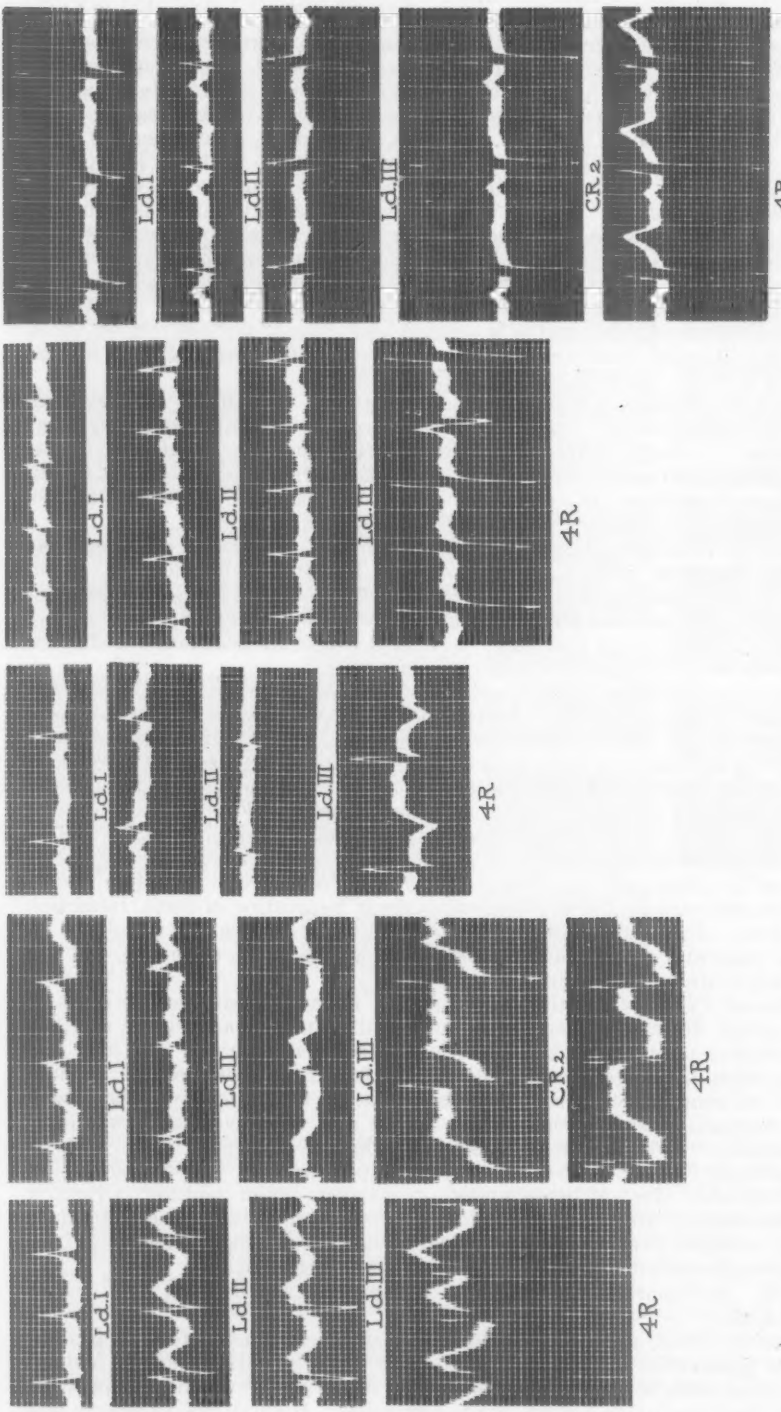


FIG. 3 (*a–e*).—Electrocardiograms of patients with pure lateral infarcts with atypical electrocardiograms.

160/110. The patient remained well and was able to work after his original coronary thrombosis until a few days before death when he had several anginal attacks. He died suddenly on Jan. 30, 1942.

Pathologic Findings. Recent and remote infarcts of lateral wall of the left ventricle. Recent thrombosis of left circumflex coronary artery and recent hemorrhage into wall of right coronary artery with organizing thrombosis. Hypertrophy and dilatation of right ventricle (470 gm.) (Fig. 1, *i*).

ECG: Regular sinus rhythm, Q_2 and deep Q_3, inversion of $T_{2,3}$. There was no deviation of the RS-T segment (Fig. 3, *e*).

Group III. Combined Infarcts. In this group we include 3 cases of recent lateral infarction accompanied by other recent myocardial infarction. In 2 cases the interventricular septum was involved; in another case there was a coëxisting recent infarction of the apex of the left ventricle. Two records show evidence of a recent posterior and basal, and septal infarction. The other case showed left bundle branch block.

Case 10. Male, age 68. *Clinical Diagnosis.* Arteriosclerotic heart disease; coronary occlusion.

Pathologic Findings. Recent infarct of lateral and posterior wall of left ventricle, and posterior part of interventricular septum. Coronary arteriosclerosis marked. Left circumflex occluded by thickening of the wall: Recent hemorrhage and thrombosis of right coronary artery. Remote arteriosclerotic occlusion of left descending coronary artery with remote infarction of anterior wall of left ventricle. Hypertrophy and dilatation of heart (490 gm.). Fibrinous pericarditis.

ECG: Evidence of posterior and basal infarction and right bundle branch block.

Case 11. Male, age 57. *Clinical Diagnosis.* Arteriosclerotic heart disease; coronary thrombosis; cardiac decompensation; right hydrothorax.

Pathologic Findings. Recent infarct of base and lateral wall of the left ventricle and anterior and apical portion of left ventricle. Severe coronary arteriosclerosis. Fresh thrombus in left circumflex coronary artery. Fibrosis of anterior and apical portion of interventricular septum. Hypertrophy and dilatation of heart (750 gm.).

ECG: Left bundle branch block.

Case 12. Male, age 50. *Clinical Diagnosis.* Arteriosclerotic heart disease; coronary occlusion; myocardial infarction, posterior and basal.

Pathologic Findings. Recent and remote infarction of lateral wall and apex of left ventricle, and posterior and basal portions of interventricular septum. Marked coronary arteriosclerosis and stenosis. Recent thrombosis of descending branch of the left coronary artery. Hemorrhage into wall. Marked fibrosis of endocardium. Acute fibrinous pericarditis. Hypertrophy and dilatation of heart (520 gm.).

ECG: Evidence of healed posterior and basal infarction and intraventricular block.

Group IV. Remote Infarcts. Four cases in this group had lateral infarcts extending into the posterior wall of the heart. Two extended into the anterior wall and only one was a pure remote lateral infarct.

Case 13. Male, age 69. *Clinical Diagnosis.* Hypertensive cardiovascular disease; generalized arteriosclerosis and dilatation of the aorta; severe heart failure; obesity; hypostatic bronchopneumonia.

Pathologic Findings. Remote healed infarct of lateral and basal portion of left ventricle. Marked arteriosclerosis and chronic fibrous pericarditis. Hypertrophy and dilatation of heart (540 gm.).

ECG: Taken before death showed auricular fibrillation. The QRS complexes were of low voltage and left axis deviation was present; a W complex was present in Lead II; the T wave was isoelectric in Leads I, II and III. There was a slight depression of the S-T segment in 4R.

Case 14. Male, age 58. *Clinical Diagnosis.* Myocardial infarction, posterior and septal; chronic bronchitis; emphysema and bronchiectasis.

Pathologic Findings. Area of scarring in central part of lateral wall of left ventricle; occlusion of left circumflex coronary artery by hemorrhage in an arteriosclerotic placque. Remote recanalized occlusion in right coronary artery. Severe arteriosclerosis with marked stenosis. Cardiac hypertrophy (470 gm.).

ECG: On admission this showed regular sinus rhythm, low amplitude of QRS; T_2 and T_3 sharply negative; slight elevation of the S-T segment in 4R with an inverted T. Another ECG taken 2 days later showed regular sinus rhythm, prolonged P-R interval, low voltage of QRS; T_1 isoelectric, T_2 and T_3 inverted. The T wave in 4R was sharply negative.

Case 15.—Male, age 63. *Clinical Diagnosis.* Myocardial infarction, remote and recent; ventricular aneurysm; bronchopneumonia; arteriosclerotic heart disease.

Pathologic Findings. Remote infarction of anterior and lateral wall of the left ventricle with remote thrombosis of the descending branch of the left coronary artery. Marked arteriosclerosis. Hypertrophy and dilatation of heart (410 gm.).

ECG: Typical of remote anterior and apical infarction with interference dissociation.

Case 16. Female, age 64. *Clinical Diagnosis.* Hypertensive cardiovascular disease; coronary occlusion; decompensation; generalized arteriosclerosis.

Pathologic Findings. Remote infarct of apex and lateral wall of the left ventricle and apical portion of the interventricular septum. Marked stenosing arteriosclerosis. Recent thrombosis of the right coronary artery. Cardiac hypertrophy and dilatation (460 gm.).

ECG: The ECG of 3/15/41 had abnormal left axis deviation and the T wave in Lead I was diphasic. On 12/5/41, taken just before exitus, the ECG showed a prolonged P-R interval; low amplitude and notching of QRS in Leads I, II and 4R.

Case 17. Male, age 59. *Clinical Diagnosis.* Coronary occlusion; recent mid-thigh amputation.

Pathologic Findings. Remote infarction of lateral and posterior wall of left ventricle. Remote occlusion of left circumflex coronary artery; partial recanalization. Remote infarcts in the interventricular septum. Marked coronary arteriosclerosis and stenosis; mitral stenosis.

ECG: Showed auricular fibrillation and a deep Q in Leads II and III. Digitalis effect was marked. The patient had been on a maintenance dose of digitalis.

Case 18. Male, age 51. *Clinical Diagnosis.* Chronic glomerular nephritis; uremia; pericarditis.

Pathologic Findings. Remote infarct of lateral and basal wall of the left ventricle and interventricular septum. Marked coronary sclerosis and stenosis. Acute myocarditis of right auricle. Acute fibrinous pericarditis. Hypertrophy and dilatation of heart (600 gm.).

ECG: Left axis deviation and digitalis effect. (The patient was digitalized.)

Case 19.—Male, age 66. *Clinical Diagnosis.* Arteriosclerotic heart disease.

Pathologic Findings. Irregular areas of scarring of lateral and posterior wall of left ventricle. Marked arteriosclerosis and stenosis. Hypertrophy and dilatation of heart (560 gm.).

ECG: Auricular fibrillation and bigeminy with depression of S-T. This patient had digitalis intoxication.

Remote Cases. In 3 cases auricular fibrillation was present but in 1 case there was an associated mitral stenosis. The records taken showed no consistent pattern. Two records showed low amplitude of the QRS complex and in Case 13 there was a W complex in Lead II. Interference dissociation was present in 1 case. Digitalis intoxication dominated the ECG of 3 cases. Two cases showed changes of old posterior and basal infarction and 1 case of old anterior and apical infarction.

Infarction of Lateral and Posterior Wall of the Right Ventricle. CASE 20. Male, age 61. *Clinical Diagnosis.* Arteriosclerotic and hypertensive heart disease; diabetes mellitus.

Pathologic Findings. Recent and remote infarction of lateral and posterior wall of right ventricle. Recent and remote occlusive thrombosis of right coronary artery. Sclerosis of coronary arteries. Pericardial adhesions over area of infarction. Mural thrombi in right auricle and right ventricle. Cardiac hypertrophy and dilatation (650 gm.).

ECG: Regular sinus rhythm, left axis deviation, slight depression of the S-T segment in Lead I and slight elevation of the S-T segment in Lead III. Lead 4R showed a small positive wave of the initial ventricular deflection. The record suggested a posterior and basal infarct. Weinberg and Katz[12] published the ECG of a patient with infarction of the lateral wall of the right ventricle showing a T_n pattern.

Contusion of Lateral Wall of the Left Ventricle. CASE 21. Male, age 50. This case was a male who had received a close range bullet wound entering the fifth intercostal space, left mid-clavicular line and penetrating the pericardial sac in the mid-portion of the lateral wall of the left ventricle. There were irregular, slightly depressed and elevated areas 3.5 cm. in diameter, which showed acute focal interstitial myocarditis. Acute fibrinous pericarditis was also present. The ECG showed changes found in pericarditis (epicarditis).

Discussion. The atypical ECG of cases of recent myocardial infarction have been studied by many authors.[3,4,7–9,11,13] The ECG may be altered by pericarditis (epicarditis); digitalization; combined infarcts, both old and recent; massive acute infarction; hypertension; cor pulmonale;[9] involvement of the right ventricle and intraventricular block. The ECG of recent infarction may be further distorted by myocardial hypertrophy and myocardial changes secondary to rheumatic heart disease. Robb and Robb[10] suggest that combinations of infarctions of the different muscle bundles may be responsible for atypical curves. Several writers[4,5,8] mention that involvement of the subendocardial layers of the myocardium may likewise be a factor.

We have found in 4 cases of recent myocardial infarction the pattern described by Wood, Wolferth and Bellet,[14] including the high incidence of auricular fibrillation. Our findings emphasize the importance of the pattern of left lateral infarction. Further experience with extremity potentials[5] may increase the accuracy of diagnosis, especially of combined lesions.

Summary and Conclusions. 1. Nineteen cases of left lateral infarction were found in 106 cases of myocardial infarcts examined pathologically. Of these lateral infarcts, 9 were recent. In these recent cases the electrocardiograms of 4 (44.4%) showed the pattern described by Wood, Wolferth and Bellet.[14]

2. Auricular fibrillation or flutter was found in 5 of these recent cases (55.5%). This incidence may have been greater actually because all of the ECG showed auricular fibrillation or flutter to be temporary.

3. In the 5 recent cases without ECG diagnostic of lateral infarction, the changes were diagnostic of posterior and basal infarction in 3 instances. The other 2 cases showed auricular fibrillation, and in 1 of these the ECG showed slight but not diagnostic depression of the S-T segment in Lead 4R.

4. Two cases associated with infarction of the posterior and basal region of the left ventricle presented ECG dominated by the T_3 pattern. One case associated with anterior and apical infarction had left bundle branch block.

5. Seven cases of remote lateral infarction showed no characteristic pattern.

REFERENCES

1. Barnes, A. R.: Am. Heart J., **9**, 734, 1934.
2. Barnes, A. R., and Ball, R. B.: Am. J. Med. Sci., **183**, 215, 1932.
3. Bohning, A., and Katz, L. N.: Arch. Int. Med., **61**, 241, 1938.
4. Boyd, L. J., and Scherf, D.: Bull. New York Med. Coll., **3**, 1, 1940.
5. Goldberger, E.: Am. Heart J., **24**, 378, 1942.
6. Johnston, F. D., Rosenbaum, F. F., and Wilson, F. N.: The Ventricular Complex in Multiple Precordial Leads, Part II: Modern Concepts of Cardiovascular Diseases, XII, No. 7, 1943.
7. Katz, L. M.: Electrocardiography, Philadelphia, Lea & Febiger, 1941.
8. Langendorf, R., and Kovitz, B.: Am. J. Med. Sci., **204**, 239, 1942.
9. McGinn, S., and White, P. D.: J. Am. Med. Assn., **104**, 1473, 1935.
10. Robb, J. S., and Robb, R. C.: Am. J. Med. Sci., **197**, 830, 1939.
11. Saphir, O., Priest, W. S., Hamburger, W. W., and Katz, L. N.: Am. Heart J., **10**, 567, 1935.
12. Weinberg, H. B., and Katz, L. N.: Am. Heart J., **21**, 699, 1941.
13. Winternitz, M.: Am. Heart J., **9**, 616, 1933.
14. Wood, F. C., Wolferth, C. C., and Bellet, S.: Am. Heart J., **16**, 387, 1938.

ABDOMINAL AORTIC ANEURYSM

Rupture Into the Jejunum Preceded by Occult Blood in the Stool

By Glenn I. Hiller, M.D.
Resident Physician in Medicine
and
Richard M. Johnson, M.D.
Consulting Physician in Medicine
Eloise, Mich.

(From the Department of Medicine, William J. Seymour Hospital)

Probably less than 25 cases of aneurysm of the abdominal aorta with rupture and perforation into the gastro-intestinal tract have been reported to date.

In 1931 Riggs and Massey,[6] in a thorough review of the subject, were able to find 9 cases which terminated by rupture and perforation into the gastro-intestinal tract, 8 rupturing into the duodenum and 1 into the transverse colon. To this collection of cases they added another which ruptured into the duodenum. Since 1931 Scully,[8]

Neely,[4] Manson,[2] Roach,[7] Penas,[5] and Smith,[9] each reported a case with rupture into the duodenum, and Kampmeier[1] reported 1 with rupture into the stomach.

The rarity of this interesting phenomenon precludes any adequate statistical study of the symptomatology which may exist prior to fatal termination. However, the clinical findings of the case reported herein are such that they may add to those already recorded in the literature.

Case Study. The patient, a 76 year old white male, was admitted to the hospital on Dec. 2, 1942. He had enjoyed good health most of his life until 5 weeks prior to hospitalization, when epigastric pain and abdominal distention occurred with abrupt onset. At times the pain was cramping, knifelike and radiated across the upper abdomen. The pain was usually aggravated by eating solid foods. Nausea and anorexia were prominent features, and on one occasion he had vomited a large quantity of bitter tasting, greenish liquid material. Since the onset of symptoms he had lost 10 pounds in weight and complained of extreme weakness and dizzy spells. There was no history of tarry stools, dyspnea, or relief of pain by the use of antacids.

Physical examination at the time of admission to the hospital revealed an elderly, well-developed but poorly nourished individual who did not appear to be in acute distress. Temperature, pulse and respirations were normal. The head, ears, nose and throat were normal. The presence of bilateral immature cataracts precluded examination of the fundi. The chest was clear to percussion and auscultation. The heart was slightly enlarged to the left, the rate and rhythm were normal and no thrills or murmurs were noted. The systolic blood pressure was 120, diastolic 70. The abdomen was scaphoid in appearance. Moderate tenderness to palpation was present in the epigastrium. The liver was palpable 3 cm. below the right costal margin in the mid-clavicular line. No other masses and no pulsations were noted. Posteriorly, moderate tenderness to percussion was present over the region of each kidney. The genitals, extremities, reflexes and rectal examination were either normal or non-contributory.

The hospital course was characterized by constant epigastric pain and anorexia, and intermittent nausea and abdominal distention. The temperature was elevated daily as high as 102° F. An admission blood count revealed 10.5 gm. of hemoglobin per 100 cc., 4,600,000 red blood corpuscles per c.mm. and 3200 white blood corpuscles per c.mm. Five urinalyses were normal except for slight traces of albumin. Examination of the gastric contents during the fasting state revealed a normal amount of free hydrochloric acid and no occult blood. No retention of food in the stomach was present on repeated aspiration. Roentgenologic examination of the upper gastro-intestinal tract revealed no demonstrable pathology in the esophagus or stomach. The duodenal cap filled to a normal contour. At 6 hours there was a slight trace of barium in the stomach, but the remainder appeared to be localized to the terminal ileum and cecum. There appeared to be a small calcified node anterior to the third lumbar vertebra. Roentgenologic examination of the colon by means of a barium enema revealed no defects, diverticulæ or polyps. Spasm was noted in the ascending and transverse colon. A 6 foot chest roentgenogram revealed the greatest transverse diameter of the thorax to be 27.6 cm., and the greatest transverse diameter of the heart to be 17.8 cm. The left ventricle was enlarged. Calcium plaques were present in the aorta. Scarring was present in the left apex and there were numerous small calcified foci in both lung fields. There appeared to be a slight pleural effusion on the left side and pneumonitis in the base of the left lung. The guaiac test for occult blood in the stool was reported as follows: December 5, positive; December 7, slightly positive; December 11, positive; December 14, strongly positive; December 17, strongly positive.

On December 18 at 1:15 P.M. the patient was found to be semicomatose, the skin cold and clammy and the blood pressure unobtainable. A large quantity of dark red liquid feces was present in the bed. Despite immediate treatment for acute peripheral vascular collapse and acute blood loss the patient expired at 1:55 P.M.

Autopsy Report.* The left pleural cavity contained 300 cc. of straw-colored fluid. On section, each lung presented a dark mottled appearance and considerable edema. The heart weighed 350 gm. The coronary arteries showed advanced atherosclerosis with some calcification. The thoracic aorta showed a number of atheromatous plaques measuring 1 to 2 cm. in diameter. A small aneurysm measuring 2 x 1.5 x 1.5 cm. was situated 18 cm. beyond the aortic valve. The abdominal aorta also showed many atheromatous plaques which measured up to 2 cm. in diameter.

FIG. 1.—Abdominal aorta showing atheromatous ulcer with "arteriosclerotic" aneurysm.

The intima of the abdominal aorta was covered by a soft thrombus which extended vertically from a level 3.5 cm. to a level 8.5 cm. above the bifurcation (Fig. 1). The thrombus measured 2 cm. transversely

* The authors express their appreciation to Dr. S. E. Gould, Attending Pathologist, and to Dr. H. N. Ginsburg, Resident in Pathology, of the William J. Seymour Hospital, for performing the autopsy and for their aid in preparation of the pathologic report.

at its upper portion and appeared to have an average thickness of about 1 cm. Its composition appeared to be old clotted blood, partially organized blood and atheromatous material. It appeared to rest upon an old ulcerated base which measured about 4 cm. vertically and up to 3 cm. transversely. The edges of the aortic intima adjacent to the ulcer were in part thinned and in part thickened. In the thick-

FIG. 2.—Specimen showing distal portion of duodenum (below and to left of ruler) and first portion of jejunum (above and to right of ruler) with perforation of jejunum (directly above ruler). Note portion of abdominal aorta (top) and iliac arteries (bottom) in background.

ened regions, there was considerable calcium deposit. The thrombus communicated with an aneurysm which was formed by dilatation of the ulcerated base of the aorta. The aneurysm measured 6 x 5 x 4 cm. and was filled with old and recently clotted blood. The wall of the aneurysm was found to be perforated at a level about 6.5 cm. above the aortic bifurcation.

Adjacent to the inferior pole of the aortic thrombus there was an irregular area of ulceration of the intima which measured about 1.2 cm. in average diameter and which was not covered by thrombus.

Old blood clots and recently extravasated blood were present in the left retroperitoneal region. The stomach and first portions of the duodenum were normal. Much fluid and clotted blood was found in the remainder of the small intestine and in the large bowel including the rectum. The posterior wall of the jejunum showed evidence of erosion and, at a point 2 cm. from its junction with the duodenum, presented an irregular oval perforation about 1 cm. in average diameter. The long axis of this perforation was transversely disposed (Fig. 2). The mucosal edges of the perforation were soft and fairly smooth. A mass of dark blood, which had entered the lumen of the jejunum at the point of perforation, was connected with a mass of blood lying between the posterior wall of the jejunum and the aorta. The level of the perforation into the jejunum was found to be 2 cm. directly below the central point of the ruptured aneurysm. Direct communication between the jejunal perforation and the ruptured aortic aneurysm was demonstrated.

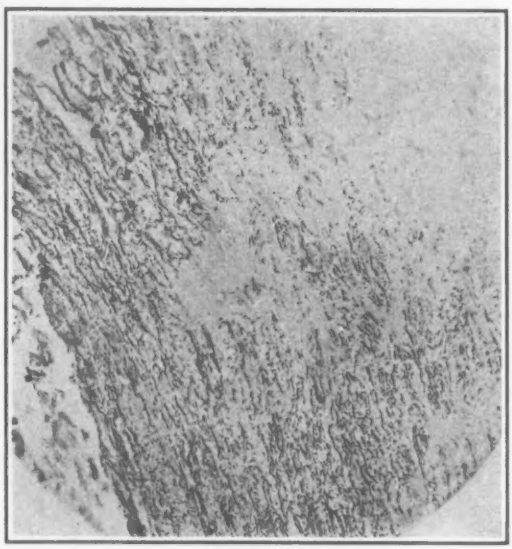


FIG. 3.—Section of aortic wall from near site of perforation showing destruction of inner two-thirds of media. Weigert elastic stain. (× 95.)

Microscopic examination of the aneurysmal aortic wall immediately adjacent to the point of rupture showed marked thinning of the media with loss of muscle and elastic tissue (Van Gieson and Weigert elastic stains), and scattered and focal round cell infiltration of the adventitia (Fig. 3). A section of the jejunal wall bordering the area of perforation showed some loss of staining of the tissue with mild round cell infiltration of the various layers of the gut wall.

The liver weighed 1500 gm. and had a "nutmeg" appearance. The spleen measured 12 x 9 x 5 cm. and weighed 175 gm. It was slightly enlarged, soft in consistency and contained an increased amount of blood.

The pathologic diagnosis was ruptured arteriosclerotic aneurysm of the abdominal aorta with perforation into the first portion of the jejunum and fatal hemorrhage into the bowel; recent hemorrhage into the left retroperitoneal tissue; small arteriosclerotic aneurysm of the thoracic aorta.

Comment. The anatomic position of the third portion of the duodenum, as it crosses the vertebral column at the level of the third lumbar vertebra, brings it into close relationship with the aorta. Furthermore, this portion of the duodenum is relatively immobilized against the vertebral column and aorta by the pancreas, the mesocolon, the suspensory ligament of Treitz and other adjacent anatomic structures. This initimate relationship probably accounts for the predilection of aneurysms of the abdominal aorta, which arise in this region, to rupture into the third portion of the duodenum rather than into other portions of the small bowel. It also seems reasonable to assume that the pressure exerted by an aneurysm against this relatively immobilized portion of the small bowel accounts for some of the clinical findings and symptoms which are present. This is, in fact, substantiated by some of the cases reported in the literature.

Mills and Horton[3] report that 8.8% of all abdominal aneurysms are accompanied by gastro-intestinal symptoms. However, in their series of 80 cases, only 32.5% were aneurysms of the abdominal aorta. Kampmeier,[1] in a detailed study of 60 patients with aneurysm of the abdominal aorta, found pain to be present in 91.6% and "indigestion" in 20% of the cases. In general, abdominal pain, usually present in the epigastrium, and indigestion followed by anorexia and weight loss are the most frequent complaints of the patient. The duration of symptoms is usually less than 1 year, but has been recorded to last as long as 4 years. Washburn and Wilbur[10] report a case of abdominal aortic aneurysm causing obstruction of the duodenum which was subsequently relieved by posterior gastro-enterostomy. These authors also cite a similar case reported by Spizharniy in 1907.

The roentgenologic findings, when present, are characterized by pressure defects on the structures adjacent to the aneurysm. Careful fluoroscopic examination of the upper gastro-intestinal tract is most important, for it may reveal and localize an extrinsic pulsating mass. Roentgenologic examination of the abdomen by means of lateral and anterior-posterior plates may demonstrate erosion of the vertebral bodies, displacement of organs or calcification in the aorta. Pyelography and barium enema examination are valuable for the same reasons —in the latter, if a pressure defect is present, it is usually in the left colon. In many instances, however, roentgenologic findings are absent or indeterminate and recourse to other clinical findings is necessary to arrive at the proper diagnosis.

The presence of occult or gross blood in the stool deserves special

attention. This finding, in the absence of any demonstrable cause and particularly when associated with gastro-intestinal symptoms, requires careful study and equally careful evaluation. Aneurysm of the abdominal aorta with pressure at some point on the gastro-intestinal tract should be included in the differential diagnosis of blood in the stool. In our review of the literature we found 3 cases in which blood was noted in the stool prior to rupture of the aneurysm with perforation into the bowel. In the case of Washburn and Wilbur,[10] occult blood was present in the stool on laboratory examination. The case reported herein showed the presence of occult blood in the stool for 13 days prior to rupture of the aneurysm with perforation into the jejunum.

Summary. A case of arteriosclerotic aneurysm of the abdominal aorta with rupture and perforation into the jejunum is reported.

Aneurysm of the abdominal aorta with pressure on the small bowel is a rare cause of blood in the stool.

REFERENCES

1. Kampmeier, R. H.: Am. J. Med. Sci., **192**, 97, 1936.
2. Manson, J. S.: Brit. Med. J., **1**, 121, 1937.
3. Mills, J. H., and Horton, B. T.: Arch. Int. Med., **62**, 949, 1938.
4. Neely, J. M.: Nebraska State Med. J., **22**, 370, 1937.
5. Penas, M. D.: Univ. of Santo Thomas J. Med., **1**, 303, 1941.
6. Riggs, T. F., and Massey, B. D.: Journal-Lancet, **51**, 413, 1931.
7. Roach, R. D.: Canad. Med. J., **41**, 173, 1939.
8. Scully, F. J.: Tri-State Med. J., **9**, 1743, 1936.
9. Smith, H. M., Jr.: Virginia Med. Month., **68**, 270, 1941.
10. Washburn, R. N., and Wilbur, D. L.: Proc. Staff Meet. Mayo Clin., **11**, 673, 1936.

A TEST FOR VASCULAR TONE IN HUMANS AND ITS APPLICATION TO THE STUDY OF VASCULAR DISEASES WITH SPECIAL REFERENCE TO THE ETIOLOGY AND PREVENTION OF THROMBOPHLEBITIS

By Meyer Naide, M.D.
INSTRUCTOR IN MEDICINE, UNIV. OF PENNA.

With the Technical Assistance of Ann Saÿen

PHILADELPHIA, PA.

(From the Peripheral Vascular Section of the Edward B. Robinette Foundation, Medical Clinic, Hospital of the Univ. of Penna.)

For a long time those working with patients with vascular disease have felt the need for an objective method of measuring vascular tone.* For the purpose of this investigation, "vascular tone" is defined as the ability of blood-vessels to constrict and dilate in response to cold and heat respectively, regardless of the mechanism involved.

We are not using the term "vasomotor tone," which is frequently employed in discussing vasoconstriction and vasodilatation, because

* Tone has been defined by Evans[5] as the "resistance muscle offers to extension." Henderson[9] defines tonus as "the peculiar vital form of muscular elasticity." Our definition of tone fits in with these in that ability of a vessel to resist vasodilatation with heat is analogous to ability of a muscle to resist stretching.

the latter phenomena, as we have observed them, are the end-result of an interplay of a variety of factors such as the degree of sympathetic tone, intrinsic smooth muscle tone of the blood-vessel wall, changes in blood volume, pressor substances and possibly other factors. We know, however, that the amount of sympathetic tone usually plays the predominant rôle in determining the state of vasoconstriction and vasodilatation.

Very little work has been done on the measurement of individual differences in vascular tone, because no clinical test was available. In patients, the diagnosis of vasospasm or abnormal vasoconstriction frequently is made solely on a clinical observation of coldness and cyanosis of the extremities in the presence of peripheral pulses. We have always regarded this diagnosis as inadequate, in that no measurement could be made of the degree of vasospasm or deviation from the normal, since the range of normal was unknown. A method has been developed by us, by which the degree of individual vascular tone can be determined by a simple clinical procedure, namely, the determination of the rate of fall in temperature of the extremities during a cool period and the rate of rise in temperature of the extremities during a period of application of moderate heat to the trunk in a constant temperature room at 20° C.

The clue to the test came from an observation made while performing routine reflex vasodilatation tests as described by Gibbon and Landis,[8] which we had commonly used to determine the presence and degree of local organic arterial occlusion, depending on the height to which the temperature of the affected extremity rose in response to (reflex) heat to the unaffected extremities. It gave us no estimate of the peripheral vascular tone of the individual. By taking routine finger temperature determinations in addition to toe temperature readings and using only *moderate* heat, we found that we had a means of grading vascular tone in any individual. The importance of finger temperature readings lies in the fact that normally there is less tone in the vessels of the fingers than in the vessels of the toes, so that by observing the response to cold and to heat at these two sites, we obtain a gradient of vascular tone or ratio of vascular response in the feet to that in the hands in each individual. This gradient of vascular tone in the toes to that in the fingers was maintained throughout all of our studies in normal individuals. An additional point that is worth emphasizing is that only by using a stimulus of moderate intensity were we able to grade vascular tone. Had we applied more heat, as, for example, the warm water bath that was used in the original Gibbon and Landis vasodilatation test, or had the electric pads been set at high heat, most normals would have vasodilated,* and we could not have distinguished those who are moderately vasospastic. Vascular tone was determined by noting the rate at which the hands and feet cool, or vasoconstrict, in a cold room; and whether they become warm, or vasodilate with heat

* We realize that the term "to vasodilate," as a verb, is not recorded by Webster, though he has defined "vasodilating" as an adjective. However, the use of "to vasodilate" is common in clinical discussion and the term has been used in this paper because of its simplicity and clarity.

TABLE 1.—REFERENCE FOR DETERMINING VASCULAR TONE

	LOW VASCULAR TONE ←						→ HIGH VASCULAR TONE
Group:	1	2	3	4	5	6	7
Toe temperature: During cool period	Remains HIGH (above 25° C.)	DROPS (below 25° C.)	DROPS (below 25° C.)	LOW at start (below 25° C.)	LOW at start (below 25° C.)	LOW at start (below 25° C.)	LOW at start (below 25° C.)
During heat period	Remains HIGH (above 25° C.)	RISES (above 30° C.)	RISES (above 30° C.)	RISES (above 30° C.)	RISES (above 30° C.)	NO RISE From temperature during cool period	NO RISE From temperature during cool period
Finger temperature: During cool period	Remains HIGH (above 25° C.)	Remains HIGH (above 25° C.)	DROPS (below 25° C.)	DROPS (below 25° C.)	LOW at start (below 25° C.)	LOW at start (below 25° C.)	LOW at start (below 25° C.)
During heat period	Remains HIGH (above 25° C.)	Remains HIGH (above 25° C.)	RISES (above 30° C.)	RISES (above 30° C.)	RISES (above 30° C.)	RISES (above 30° C.)	NO RISE From temperature during cool period

applied to the trunk. With this information we made up a simple table into which individuals can be placed on the basis of vascular tone and from which the grade of vascular tone can be determined for any individual (see Table 1). With this classification we were able to obtain the range in ability to vasoconstrict and vasodilate in normal individuals. Thus we have a basis of comparison for determining the presence or absence of abnormal vasoconstriction or vasodilatation in patients.

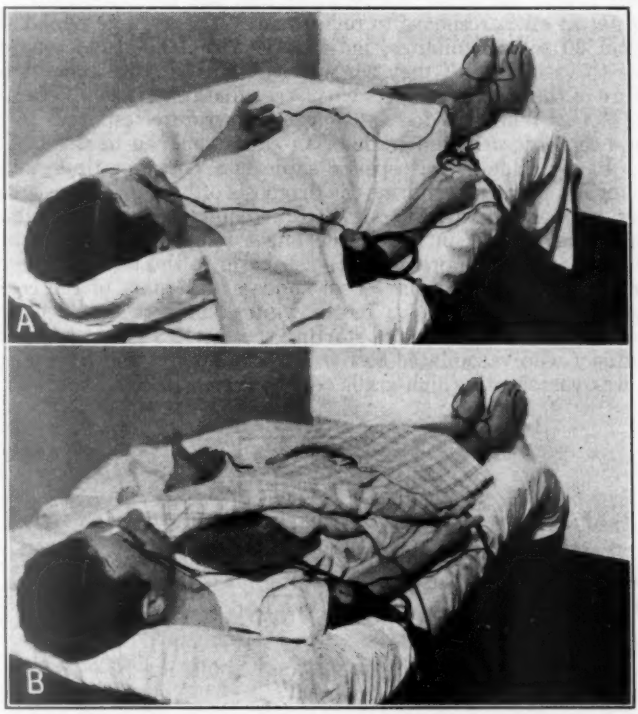


FIG. 1.—*A*, Test for vascular tone. Period of cooling. Temperature of room 20° C. *B*, Period with reflex heat. Temperature of room 20° C. Corner of blankets turned up to show position of electric pads.

Method. The subject is asked to omit the meal and any medication before the test. The test is described to the patient in general terms so that there will be no fear. The patient is asked to void before entering the test room to lessen nervous tension during the test. After entering the cold room, the temperature of which is maintained at 20° to 22° C. by a cooling unit, the subject undresses completely and puts on a light gown or sheet and lies in the supine position, his legs and arms being uncovered (see Fig. 1*a*). Thermocouples are attached to the first and third toes of each foot and the third fingers of each hand. The following routine measurements are taken 15 minutes after the patient lies down and every 10 minutes or so thereafter, longer intervals of time sufficing after the initial rise in skin temperature is observed following the application of heat: the temperature at each thermocouple; mouth temperature; blood pressure and pulse rate. When the toe and finger temperatures have dropped to as low a level as it appears they can fall (20° to

22° C.), requiring 30 to 60 minutes, 2 ordinary electric heating pads* are applied to the trunk, covering it from the pubis to the neck. Two blankets are then used to cover the patient, excluding, however, the feet and ankles, arms and head (see Fig. 1*b*). The pads are turned on 5 minutes prior to being used so that they are warm when placed on the patient. The switch on the pads is set at medium heat. Readings are then taken as during the cold period, with the exception that time of onset and degree of sweating are recorded. Blood pressure and pulse rate determinations are not necessary in the routine grading of vascular tone, but have been taken by us to observe the changes taking place during the cool and warm periods in individuals with different degrees of vascular tone. If the subject has high-grade vascular tone (the vasospastic type), the finger temperature and the toe temperature will rise slowly or not at all in response to reflex heat. The average period with heat ranges from 60 to 150 minutes, individuals with high-grade tone requiring more time to vasodilate, if they can vasodilate at all with reflex heat. The temperature of the toes and fingers when vasodilatation is complete is between 30° and 34° C. When the toe and finger temperature responses to cold and heat have been obtained, the grade of vascular tone can be determined from Table 1. In some highly vasospastic subjects a posterior tibial nerve block with 3 cc. of 2% procaine confirms the diagnosis of high-grade vascular spasm. In testing normal individuals, one hardly requires a posterior tibial nerve block, since the manner in which the finger temperature responds to cold and heat will confirm the presence of vasospasm in the toes. Only the vasospastic individuals normally have cool hands at the start of the cool period; this is readily seen in Table 1. In the winter, subjects should be kept in a warm room for 30 minutes before starting the test. Typical tests done on a normal subject who vasodilated easily (low-grade tone) and on a normal subject who was vasospastic (high-grade tone) are seen in Figure 2.

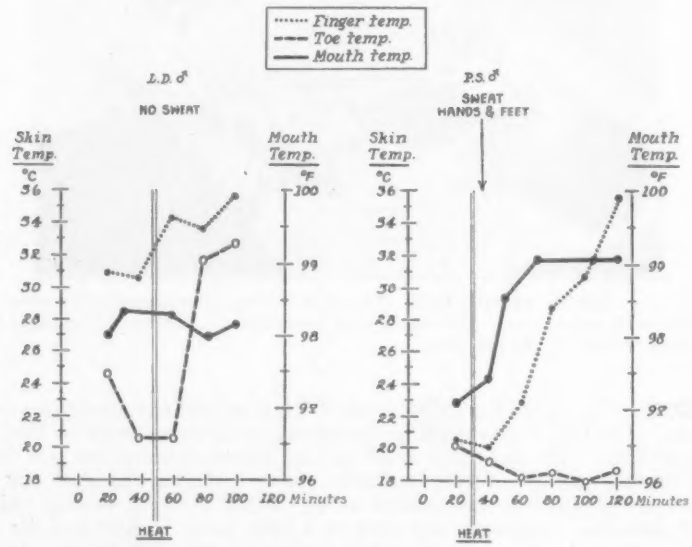


FIG. 2.—Responses during test of subject L.D. with low vascular tone (Group 2) and subject P.S. with high vascular tone (Group 6).

Results. The test has been performed on 172 individuals (including 119 patients and 53 normals as controls).

* Westinghouse warming pad (cloth covered) 60 watts, 95-125 volts.

Normal Individuals. It was found early that normal subjects varied enormously in vasoconstrictor and vasodilator ability. The 53 normals tested had all grades of vascular tone with the exception of the most vasospastic grade (Table 2, Group 7). Normal individuals range all the way from those who are so dilated as the result of low vascular tone that they cool with difficulty in a cold environment, to those individuals who are always cold and respond slowly or not at all to reflex heat. The latter group of individuals is so vasoconstricted that they appear to behave no differently to reflex heat than patients with severe organic arterial occlusion in the legs.

TABLE 2.—PERIPHERAL VASCULAR TONE IN 53 NORMALS AND 119 PATIENTS

	LOW TONE ←						→ HIGH TONE
Diagnosis *Group:*	1	2	3	4	5	6	7
Normals (controls)	3	8	10	4	19	9	0
Acrocyanosis	..	..	..	..	1	2	
Arteriosclerosis	1	6	3	2	3	2	
Causalgia	..	..	..	..	1	2	
Hypotension (postural)	1						
Hypertension	..	3	1	3	2	6	1
Hyperthyroidism	..	..	..	..	..	..	1
Hypothyroidism	..	1	..	..	1		
Pernio	..	..	..	..	1	2	
Poliomyelitis	..	..	..	..	..	1	
Psychoneuroses	..	..	2	1			
Raynaud's disease	..	..	..	..	2	1	
Retinal angiospasm	..	..	..	..	..	3	
Scalenus anticus syndrome	..	..	..	..	..	1	
Scleroderma	..	..	..	..	1	4	1
Thrombophlebitis	..	1	..	..	8	8	
Vasospasm (patients)	..	..	..	..	3	4	

As the result of our observations we have been able to divide normal individuals into 2 main groups on the basis of their vascular tone. Those in Groups 1, 2 and 3 have low vascular tone as compared with those in Groups 5, 6 and 7, who have high vascular tone and are looked upon as being the vasospastic types. Group 4 is an intermediate group. Twenty-one of the 50 normals fell into Groups 1, 2 and 3. Twenty-eight of the 50 fell into Groups 5 and 6 (vasospastic groups). Too few normal subjects have been tested to attach any significance, statistically, to the number and percentage in each group. The response of male and female subjects during the vascular tone test is summarized in Table 3.

An individual will often prove to be vasospastic despite lack of a subjective history of cold hands and feet.

Patients With Vascular Disease (see Table 2). As might be expected, patients with known vasospastic diseases fell into Groups 5, 6 and 7. The 3 patients with Raynaud's disease fell into Groups 5 and 6. The 3 patients with acrocyanosis fell into Groups 5 and 6. Six patients with scleroderma fell into Groups 5, 6 and 7. Three patients with pernio fell into Group 6. Three patients referred by ophthalmologists with a diagnosis of retinal angiospasm all fell into Group 6.

Of the 172 tests done, in only 3 patients was the response such that they could not be classified according to Table 1. In these patients

there was a disproportion in grade of vascular tone in the hands and feet, vascular tone being either much higher in the hands than in the feet, or very high in the feet and very low in the hands. One of these 3 patients had severe arthritic changes in the lower spine, which explained the local vasospasm in the legs. The other 2 patients had vasospasm in the hands, which was not true Raynaud's disease or acrocyanosis, and which we termed simple vasospasm of unknown etiology, possibly on the basis of a local mechanical or neurologic condition. It is conceivable that some patients may have low vascular tone in the legs and yet have vasospasm in the hands on the basis of a scalenus anticus syndrome, cervical rib, hemiplegia, pneumatic hammer disease, frost-bite or traumatic arterial spasm. When the response in either the hands or feet during the test is such that the patient cannot be placed anywhere in Table 1, that individual has a pathologic grade of vascular tone such as purely local vasospasm or organic occlusion in the non-conforming extremities.

Thrombophlebitis. An unexpected finding was that the great majority of patients with thrombophlebitis were in the vasospastic groups. Sixteen of 17 patients tested had a high grade of vascular tone, falling into Groups 5 and 6. The 1 patient in the low vascular tone group had much milder symptoms of thrombophlebitis, and when seen a year later had recovered spontaneously. All of these tests were done in the warmer months. We then obtained from our files the records of the cases diagnosed thrombophlebitis seen in the year prior to the start of this investigation. Eighteen of the 20 patients seen had a history or evidence of cold feet or cold feet and hands. In addition, 2 patients who had been labeled by us clinically as being vasospastic, have since been operated upon and have developed thrombophlebitis.

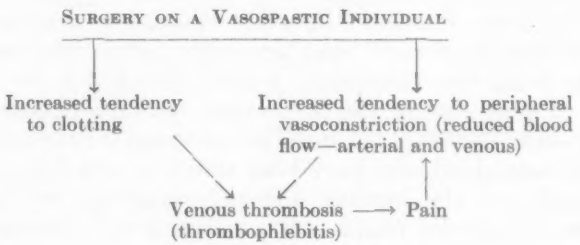

Surgery on a Vasospastic Individual
Increased tendency to clotting
Increased tendency to peripheral vasoconstriction (reduced blood flow—arterial and venous)
Venous thrombosis (thrombophlebitis)
Pain

Fig. 3

We know that a certain percentage of normal individuals, the vasospastic normals, when vasoconstricted, cannot vasodilate for hours, even with electric pads, during which period blood flow is greatly reduced in the extremities. Furthermore, the veins also participate in the peripheral vasoconstriction. When a vasospastic individual is subjected to the vasoconstrictor, stimuli arising from abdominal and pelvic surgical procedures, which include anxiety and pain, plus the shortening of blood coagulation time, which occurs for several days following surgery, we have an ideal set-up for thrombosis to develop in the veins (see Fig. 3). In addition, once thrombophlebitis is

initiated, pain may cause further reflex vasoconstriction and further venous thrombosis. The knowledge that it is the individual with high vascular tone who is most susceptible to thrombophlebitis may answer the question that Evans[6] asks in a recent paper on thrombophlebitis: "Why do these epidemics of pulmonary embolism come in winter time?" The answer well may be that we are all more vasoconstricted in the winter, and the vasospastic individuals even more so.

One of the reasons that phlebitis occurs almost always in the legs may be that it is in the lower extremities that vascular tone is greatest. Veal and Hussey[17] found that operative manipulations within the abdominal cavity cause an immediate rise in venous pressure in the saphenous vein without affecting the pressure in the antecubital vein. Davis, Gilman and Freedberg[4] found marked increases in venous pressure in the veins of the foot during abdominal operations.

It is possible that measures directed to prevent vasoconstriction in the legs may be of importance in reducing the incidence of postoperative thrombophlebitis and pulmonary embolism. These measures would include prevention of chilling such as by insufficient blankets or permitting the patient to be uncovered or in a draft. Prevention or rapid relief of shock to prevent peripheral vasoconstriction would be indicated. The recent introduction of leg exercises has reduced the incidence of pulmonary embolism considerably (Krebs;[11] Evans[6]). This type of exercise, by increasing blood flow and producing hyperemia, aids in maintaining vessels in a state of vasodilatation. Smith and Allen[16] found a reduced venous flow in the extremities postoperatively. Walters[18] has advised the use of thyroid to increase blood flow in the extremities postoperatively. Leriche[13] and also Ochsner and DeBakey[14] have popularized paravertebral ganglia block with procaine for acute thrombophlebitis. Their rationale for this is that the venous thrombus causes reflex arterial and venospasm, which plays a primary rôle in producing the full-blown picture of thrombophlebitis. However, knowledge of the fact that the vasospastic individual is the one most likely to be thrown into reflex vasospasm, and that he happens also to be the one most susceptible to thrombophlebitis, suggests that the vasospasm plays a rôle not only after the development of the venous thrombus, but in bringing it about. By looking upon thrombophlebitis as a disease in which the vasospastic state or preliminary abnormal vasoconstriction, venous and arterial, plays an important rôle, our concept of it becomes clearer, and prevention placed upon a more rational basis. The importance of prevention of thrombophlebitis is demonstrated by Gibbon's[7] statistical analysis that of every 100 postoperative deaths, 8 are due to pulmonary embolism.

Thromboangiitis Obliterans. Nine of 32 patients with thromboangiitis obliterans were in the groups with low vascular tone, 1, 2 and 3. Prior to the development of this test for vascular tone, one could only have an impression that patients with this disease had or had not vasospasm. By measuring finger temperature responses to cold and heat, we can tell whether these patients are types with high or low vascular tone, even though they have severe organic arterial occlusion in both

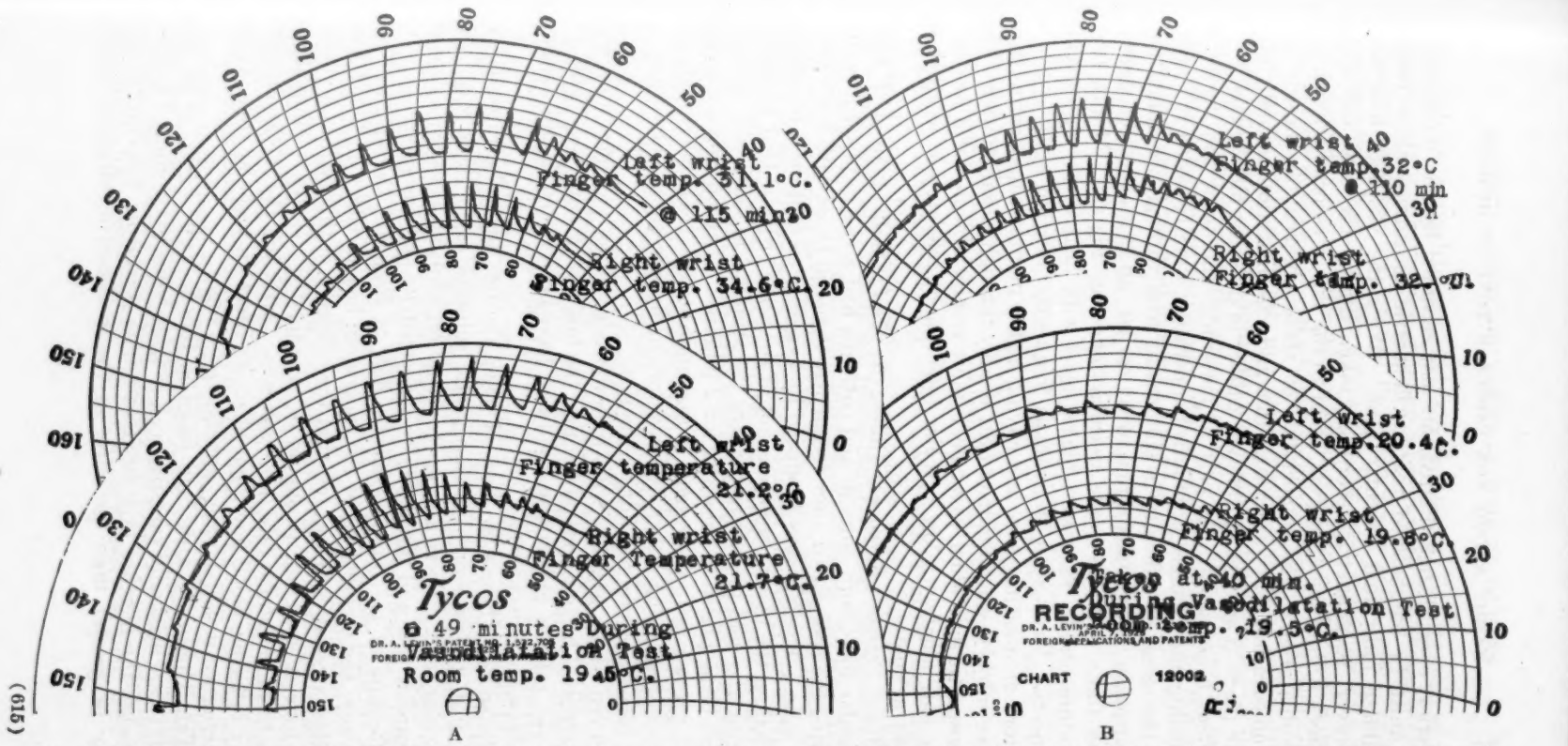
legs, or if both legs have been amputated. The 5 female patients with thromboangiitis obliterans were all vasospastic.

Emotional Influences on Vasoconstriction and Vasodilatation. The effect of emotions on vascular responses was often observed during the test. Tension produced in a patient, on being told that a posterior tibial nerve block was to be done, often caused a drop of 2° to 6° C. in toe and finger temperatures as the result of reflex vasoconstriction. The drop in temperature was always greater in the upper extremities. Conversation concerning subjects which worried the patient would cause a drop of several degrees in skin temperature. Vasoconstriction in response to emotional stimuli was more prominent among vasospastic individuals than among those with low-grade vascular tone.

TABLE 3.—PERIPHERAL VASCULAR TONE IN 50 NORMALS AND 121 PATIENTS

	Male	Female
Normals:		
Low tone (Groups 1–3)	11	8
Group 4	2	3
High tone (Groups 5–7)	9	16
Patients:		
Low tone (Groups 1–3)	22	5
Group 4	5	1
High tone (Groups 5–7)	42	46

Location of Vasoconstriction and Vasodilatation. A question which arises in our measurement of constriction and dilatation is that of its location along the vascular tree. Are the vessels that are constricting and dilating large arteries, small arteries, arterioles or capillaries? By combining oscillometric recordings with the vascular tone test, a clue is obtained in some patients. Oscillometric recordings are taken at the wrist and ankle. In vasospastic individuals (normals and patients) oscillometric readings or pulsations were usually small during the cool period. With vasodilatation the pulsations, as recorded by the oscillometer, increased markedly in some subjects, but increased only slightly or not at all in others. The interpretation of this can be only that when pulsation does not increase with vasodilatation, the increase in blood flow must be accomplished through dilatation of vessels that are smaller than can be recorded by the oscillometer. On the other hand, with increased pulsation during vasodilatation, the increase in blood flow must have been accomplished through dilatation of arteries of the caliber of the radial and ulnar, or dorsalis pedis and posterior tibial, which are known to record on the oscillometer. In an individual whose vasoconstriction and dilatation occurs in vessels smaller than the caliber of the wrist and ankle arteries, the oscillometric readings will be moderately large and of the same size during vasoconstriction and vasodilatation (Fig. 4). In this type of vasospastic individual, only a vascular tone test as described will reveal the presence of high-grade vasoconstriction. It is interesting to observe that a patient with organic arterial occlusion and an adequate collateral circulation will have no increase in zero oscillations, even though the skin temperature rises to normal during vasodilatation. This is an objective demonstration that vessels of a lesser caliber than the major



(916)

FIG. 4.—*A, High vascular tone* (Group 6). Oscillometric readings unchanged during vasoconstriction and vasodilatation in individual who vasoconstricts in small arteries or arterioles. *B, High vascular tone* (Group 6). Oscillometric readings increased during vasodilatation in individual who vasoconstricts in arteries of large caliber.

arteries, even though dilated, are not recorded by the oscillometer. It must be emphasized that oscillometric recordings alone cannot evaluate individual vascular tone. With the vascular tone test, however, oscillometric recordings taken during the cool and warm periods will, in some subjects, point to the site of vasoconstriction and vasodilatation. The importance of these observations lies in the demonstration that vasoconstriction and vasodilatation normally may take place in arteries of different caliber in different individuals.

Heat Elimination. As part of the study, the onset and degree of sweating and changes in mouth temperature were recorded routinely. As the result of difficulty in eliminating heat through vasodilatation, vasospastic individuals often sweat earlier, and to a greater degree, than those with low-grade vascular tone (see Fig. 2). Mouth temperature usually rises to a higher level with heat in the vasospastic subjects. Vasospastic individuals frequently, but not always, give a history of sweating more and having higher mouth temperatures than those subjects who eliminate heat readily through vasodilatation. The vasospastic individual, as a rule, is more comfortable in warm weather. The individual with low vascular tone cannot tolerate hot weather as easily as cold.

Blood Pressure Responses During the Test. Individuals with high vascular tone, both normals and patients, had a rise in blood pressure during the cool period more frequently than did those with low vascular tone. The stimulus produced by exposure to cold for a prolonged period on the blood pressure is not of the same order as that produced during the cold pressor test where the stimulus is sharp and short, a hand being placed in ice-water for 2 minutes. The significance of the cold pressor test, at present, is uncertain except that individuals are classified as being either hyporeactors or hyperreactors, according to the blood pressure rise during the test.

Seven of 16 patients with hypertension whose vascular tone was determined by our method fell into the low tone groups (see Table 2). As yet, too few hypertensive subjects have been tested in this manner to draw any conclusions.

Pulse Rate During the Test. During the test the pulse rate rose or fell just as frequently in vasospastic subjects as in those with low vascular tone. There appears to be no relationship between a change in cardiac rate and the ability to vasoconstrict and vasodilate.

Relation of the Basal Metabolic Rate to Response During the Test. Because the metabolism of the individual has an effect on blood flow in the extremities, it was felt that the influence of this factor on vascular tone, as we grade it, should be investigated. Table 4 summarizes the basal metabolic rate in 31 subjects. Although the metabolic rate may influence blood flow somewhat, its effect on vascular tone, as we determined it individually, appears to be slight.

The 3 patients with high basal metabolic rates (+17, +34 and +43) were markedly vasospastic, 2 of them being in Group 7. In such patients the increase in sympathetic tone producing vasoconstriction may be greater than the effect of the increased metabolism, which

would otherwise tend to produce vasodilatation. Twenty-nine of the 31 basal metabolic rates were done on subjects with high vascular tone. Seventeen of these had normal basal metabolic rates. In 3 of the 7 patients with high vascular tone and a low basal metabolic rate, the figure was only −11. Although vascular tone, *per se*, does not appear to be greatly influenced by the basal metabolic rate, it is possible that a low basal metabolic rate in a vasospastic individual will further reduce blood flow and be an additional factor in predisposing an individual to postoperative thrombophlebitis. The use of thyroid postoperatively to prevent thrombophlebitis, as recommended by Walters, certainly appears rational in such a situation.

TABLE 4.—BASAL METABOLIC RATE AND VASCULAR TONE IN 6 NORMALS AND 25 PATIENTS

	Low B.M.R. below −10	Normal B.M.R. −10 to +10	High B.M.R. above +10
Low vascular tone (Groups 1–4 incl.)	1 patient	1 normal	None
High vascular tone (Groups 5–7 incl.)	7 patients 2 normals	14 patients 3 normals	3 patients

Vascular Tone and Blood Volume. As warm weather approaches, peripheral vasodilatation increases in order that body temperature will remain normal. Bazett[1] has found that the blood volume increases in the spring to take care of both internal organ needs and also that of continued increased peripheral blood flow. In the fall, however, with gradual peripheral vasoconstriction as the result of lower environmental temperature, the blood volume decreases. Since this is true, it may be that vasospastic individuals have lower blood volumes than individuals with low vascular tone.

Reactions of the Pupil During the Vascular Tone Test. Early in this investigation we observed that individuals who fall into the vasospastic group usually have strikingly large pupils, particularly the group with thrombophlebitis. As a result of this observation we made routine measurements of the diameter of the pupil during vasoconstriction and reflex vasodilatation. The light surface overhead, at which the patient's vision was directed during measurement of the pupils, was kept constant at 2.69 millilamberts throughout the test. The diameter of the pupil was measured with the pupillometer described by Bourbon.[2] Pupils measuring 5 mm. or more were considered large under the light conditions of this investigation. During vasodilatation the pupils became smaller in most of the patients and normals—markedly so in some, less so in others. Langworthy has pointed out that the pupil dilates when the vessels of the iris constrict and becomes smaller when the vessels fill with blood. We know that constriction of the blood-vessels in the iris is brought about through increased sympathetic tone, and for this reason we consider the larger pupil, in individuals with more than average tendency to peripheral vasoconstriction, additional clinical evidence of increased sympathetic tone as the cause of increased peripheral tone. A few vasospastic individuals had small pupils. In them, increased vascular tone did

not appear to be of sympathetic origin. This was true in a few of the normal individuals, as well as in 2 of the 3 patients with Raynaud's disease whom we have tested. This fits in with the recent concept of Lewis and others that the fault in Raynaud's disease lies primarily in the blood-vessel wall and not in increased sympathetic tone.

Discussion. This test on normal individuals and patients has given us a measuring rod for vascular tone, which permits us to investigate problems where it plays a rôle.

It is probable that the behavior of a vasospastic individual with peripheral organic arterial disease differs from that of an individual with low vascular tone with the same degree of organic arterial disease. Clark[3] has observed the disappearance of arterioles in the rabbit's ear with "lessening of blood flow—persistent maintenance of a completely contracted condition." On the other hand, he found that increased blood flow may lead to the formation of numerous arteriovenous anastomoses in stable vascular networks. This suggests that the rate of development and patency of collateral vessels in patients with organic arterial disease may be related to their peripheral vascular tone.

The finding that many normal persons are so vasoconstricted that they may be easily confused with patients with peripheral vascular disease makes it quite conceivable that occasionally a vasospastic individual will be needlessly sympathectomized. This could occur should he complain of symptoms in the extremities on a basis other than vascular disease and where the examiner could find no pulses in the feet and no rise in toe temperature with an ordinary vasodilatation test which measured only the changes in the affected extremities. However, this type can be differentiated from patients with organic arterial disease by observation of the fact that the hands also participate in the vasoconstriction and can disclose the diagnosis of high-grade vascular tone. Furthermore, nerve block with procaine will cause vasodilatation in the vasospastic individual who fails to respond to reflex heat, but not in the patient with organic arterial occlusion. It may be asked why nerve block in a vasospastic individual will not suffice for determination of vascular tone. A glance at Table 1 discloses that only the individuals in Groups 6 and 7 are proper subjects for this test, as it is only in these 2 groups that the extremities fail to respond to reflex heat. None of the individuals in Groups 1, 2, 3, 4 and 5 could be differentiated by nerve block alone, yet they represent tremendous individual variations in ability to vasoconstrict and vasodilate.

The importance of the part that vasospasm plays in the etiology of thrombophlebitis has been disclosed by the test. It is interesting that thrombophlebitis is common in the Scandinavian countries, where vasoconstriction would be assumed to be the result of a cold climate.

Various problems are yet to be worked out relating the degree of vascular tone to other pathologic conditions. For example, what relationship is there, if any, between the degree of vascular tone and the ease with which shock develops? Does the individual with low

vascular tone have a more or a less efficient mechanism to withstand shock? What is the significance of the fact that some hypertensive patients fall into the low vascular tone group, whereas others are vasospastic? What relationship is there, if any, between the information obtained by this test and that obtained by the cold pressor test? Individuals who proved to be hyperreactors with the cold pressor test did not show signs of vasospasm during the vascular tone test. The complexity of the problem is illustrated by the fact that during the cold pressor test (placing a hand in ice-water for 1 minute while observing blood pressure responses in the opposite arm) we found little or no drop in skin temperature of the toes, even in a hyperreactor. Yet telling such a patient that he will be stuck with a needle for a posterior tibial nerve block causes a drop of 2° to 6° C. in skin temperature, which reflects a considerable reduction in blood flow in the hand. Furthermore, leaving such a patient in a cool room for 30 to 60 minutes results in a 10° C. drop in toe and finger temperatures, demonstrating that different stimuli have different effects on blood-vessels. The vascular tone test offers us a measure for evaluating the rôle that individual vascular tone or ability to vasoconstrict and vasodilate may play in a variety of diseases. We are continuing the typing of normal individuals and patients with various vascular diseases with the hope that the separation of individuals into vascular types may help us in the study of the etiology of certain vascular diseases and the varying response to therapy in different patients with the same disease.

Summary. A clinical method for the determination of "vascular tone" in humans is described.

Results of vascular tone typing, carried out on 172 individuals, have revealed the wide range of vascular tone in normal persons and patients and its significant rôle in the etiology and course of certain vascular diseases and in the selection of appropriate therapy.

The importance of vasospasm in initiating thrombophlebitis or phlebothrombosis has been disclosed by the test.

This test can indicate whether vasoconstriction and vasodilatation in different individuals is taking place in large or small vessels.

The relation of vascular tone to basal metabolic rate, blood volume, blood pressure, cardiac rate, heat elimination, emotional stimuli and size of the pupil have been studied and discussed.

REFERENCES

1. Bazett, H. C.: J. Am. Med. Assn., **111**, 1841, 1938.
2. Bourbon, D. P.: Am. J. Ophth., **25**, 1107, 1942.
3. Clark, E. R.: Physiol. Rev., **18**, 229, 1938.
4. Davis, D., Gilman, S., and Freedberg, A. S.: New England J. Med., **229**, 272, 1943.
5. Evans, C. L.: Physiol. Rev., **6**, 358, 1926.
6. Evans, J. A.: Ann. Int. Med., **17**, 970, 1942.
7. Gibbon, J. H., Jr.: Pennsylvania Med. J., **42**, 877, 1939.
8. Gibbon, J. H., Jr., and Landis, E. M.: J. Clin. Invest., **11**, 1019, 1932.
9. Henderson, Y.: Medicine, **22**, 223, 1943.
10. Hines, E. A., Jr., and Brown, G. E.: Am. Heart J., **11**, 1, 1936.
11. Krebs, J. M.: Am. J. Obst. and Gynec., **44**, 73, 1942.

12. Langworthy, O. R.: Arch. Neurol. and Psychiat., **50**, 590, 1943.
13. Leriche, R., and Kunlin, J.: Presse méd., **42**, 1481, 1934.
14. Ochsner, A., and DeBakey, M.: J. Am. Med. Assn., **114**, 117, 1940.
15. Russek, H. I.: Am. Heart J., **26**, 398, 1943.
16. Smith, L. A., and Allen, E. V.: Proc. Staff Meet. Mayo Clin., **16**, 53, 1941.
17. Veal, J. R., and Hussey, H. H.: Surgery, **7**, 809, 1940.
18. Walters, W.: Surg., Gynec. and Obst., **50**, 154, 1930.

ACUTE THROMBOCYTOPENIC PURPURA IN INFECTIOUS MONONUCLEOSIS

Report of a Case

By Putnam C. Lloyd, Major, M.C., A.U.S.
NEW YORK, N. Y.

(From the Second General Hospital.)

In the past 10 or 15 years many additions have been made to our knowledge of infectious mononucleosis, and the protean manifestations of this somewhat mysterious disease entity are becoming more and more familiar. The occurrence of various hemorrhagic phenomena is now recognized as not being extremely unusual, although in earlier descriptions of mononucleosis it was stated categorically that purpuric and petechial eruptions did not appear.[4] Epistaxis, however, has always been a common incident in the course of the disease and as early as 1895 observers recorded that nosebleeds might be the precursor of glandular fever.[1] Tidy and Daniel[7] reported a school epidemic of 24 cases of which 8 had one or more epistaxes at various stages of the illness. Similarly hematuria has been a fairly common manifestation of infectious mononucleosis and in a series of 270 cases collected in 1921 as many as 6% were found to show urinary bleeding.[8] The hematuria, while it may be severe, is not usually associated with casts or functional disturbance and rarely if ever is the precursor of acute nephritis. Rectal bleeding has also been reported but is seldom a prominent feature.

At present the development of hemorrhagic skin eruptions is recognized as an episode of moderate frequency and merely constitutes one of a great variety of rashes which have been described in this disease. Petechial and purpuric hemorrhages may occur anywhere in the skin or mucous membranes, larger ecchymoses may be seen, and in some cases a positive tourniquet test may be found—in all these instances the blood platelets being normal in number and no other indications of a hemorrhagic diathesis being present.[1]

The occurrence of a true acute thrombocytopenic purpura in conjunction with infectious mononucleosis is, however, exceedingly rare, and in fact only a very few unimpeachable cases may be found in the literature. Williams[9] in 1931 described his own experience with glandular fever in which he developed a purpuric rash with a positive tourniquet test and prolonged bleeding time, but no platelet count was done. Minot[6] in 1936 reported 3 cases in which severe thrombocytopenic purpura was accompanied by lymphocytosis and some varying

degree of lymph node enlargement. In only 1 of these was the heterophil agglutination test performed, however, and it proved to be negative. Downey and McKinlay[3] in presenting a group of 9 cases described 2 in which purpuric phenomena appeared, but again no platelet counts were made and no gross hemorrhages occurred. On the other hand, Cottrell's group of 12 cases contained 1 in which a platelet count of 77,600 was reported but no hemorrhagic manifestations were described,[2] and in another instance a platelet count of 45,000 was found in the absence of any evidence of bleeding.[1]

Perhaps the most authentic case of true purpura and mononucleosis is that recorded recently by Magner and Brooks[5] in which hematuria, bleeding gums, purpuric eruption, prolonged bleeding time, and estimated reduction in platelets were combined with lymphocytosis, palpable spleen, moderate enlargement of the inguinal nodes, and a Paul-Bunnell test of 1:800, the entire condition clearing up in 6 to 8 weeks. Inasmuch as this clinical picture is one of extreme rarity, the addition of a similar instance to the list seems warranted and the present case is herewith reported:

Case Report. M. S., age 30, 2d Lt., Chem. Warfare Dept., U. S. Army, Jewish, was admitted to the 2d Gen. Hosp. on Oct. 15, 1942, complaining of weakness, fever, and sweats of 3 weeks duration, and red spots appearing on tongue and lips in the preceding 3 to 4 days.

Family History. Several members of his family had hay fever. His mother had rheumatism. There was no history of tuberculosis, diabetes, cancer, or diseases of the blood.

Personal History. He had been a pharmacist's assistant in civilian life and had been in the army 22 months. He thought he had lost about 4 to 5 pounds in the past 6 months. He smoked 8 to 10 cigarettes daily and used alcohol rarely.

Past History. His general health had been excellent. He had had no serious illness or operations, no allergic reactions, no tendency to bleed or bruise easily, and no disease involving the lymph nodes. His cardiorespiratory system had been essentially negative. There were no gastro-intestinal symptoms save occasional heartburn and what he called sour, nervous stomach. He had never been jaundiced. He had had no symptoms referable to the genito-urinary tract and venereal disease was denied. It is of interest to note that the patient passed an army insurance examination about 3 weeks before admission to the hospital.

Present Illness. He felt in his usual state of good health until about mid-July when after 2 or 3 days of being unusually tired he noticed that his urine showed a pinkish discoloration. He did not seek medical advice and after a short period of rest the condition cleared up. Thereafter he felt well until in early September he experienced gradually increasing fatigue and weakness, without localizing symptoms. About the first of October he began to feel feverish at times and to have night sweats. Thinking he had a grippy cold he stayed in quarters for 3 or 4 days, but his temperature reached 102° F. and on Oct. 10, 1942, he was admitted to the 180th Station Hospital where a diagnosis of acute bronchitis was made and he was treated with ephedrine nose drops and grippe capsules containing aspirin, phenacetin and caffeine. At no time did he receive any quinine, sedormid or sulfonamide drugs.

On the 3rd hospital day he complained of several sore spots in his mouth and was found to have numerous hemorrhagic blebs on his tongue and buccal mucosæ and a few petechiæ scattered over his body. He continued to have fever reaching 101° F. daily and was weak and lethargic. More ecchymotic spots appeared on his lips, tongue and oral mucosa, he had nosebleeds, and

TABLE 1.—LABORATORY FINDINGS

Date (1942)	Hgb. (%)	R.B.C. (mill. per c.mm.)	W.B.C. (thous. per c.mm.)	Segmented (%)	Lym. (%)	Mono. (%)	Eos. (%)	Baso. (%)	Platelets (thous. per c.mm.)	Sediment rate (mm./1 hr.)	Paul-Bunnell test	Urine	Stool
Oct. 15	94	4.8	11.8	35	54	10	0	1	66	50	..	Dark red; grossly bloody; albumin 4+	Guaiac 4+
19	..	..	..	..	..	..	..	..	..	..	..	Grossly bloody	Guaiac negative
21	..	4.1	8.8	20	77	2	1	..	..	..	1:512		
24	..	..	..	..	..	..	..	..	..	..	..	Occ. R.B.C.	
25	80	3.9	7.9	38	58	3	..	1	76				
Nov. 2	102	4.7	8.3	44	52	3	1	..	116	33	..	Negative	
13	92	4.6	10.4	58	34	5	2	1	..	..	..	Negative	Neg. for ova and parasites; no pathogens
20	..	..	13.3	61	32	5	1	1	148	25	..	Negative	
30	..	..	9.8	50	46	3	1	..	174	27			
Dec. 5	..	..	9.1	51	35	10	2	2	202	..	..	Negative	
12	..	..	8.5	60	38	1	1	..	..	..	1:64		

Blood Smears.—Previous to November 20 showed numerous large lymphocytes and mononuclears with many atypical forms. No lymphoblasts seen. Platelets were extremely scarce in the early smears.

Additional Laboratory Work.—October 15: Blood culture sterile. Bleeding time, 1 minute. Clotting time, 6 minutes. October 22: Total serum protein, 7.06 mg. per 100 cc.; serum albumin, 4.13 mg. per 100 cc.; serum globulin, 2.93 mg. per 100 cc.; icteric index, 6; serum phosphorus, 3.56 mg. per 100 cc.; serum phosphatase, 6.72 mg. per 100 cc. October 25: Fragility test normal.

Sternal Puncture.—October 21: Smear of the sternal marrow shows numerous atypical mononuclear cells similar to those seen in the peripheral blood. No abnormality of the various bone marrow elements is detected.

began to pass grossly bloody urine. Two days later he was transferred to this hospital for further study.

On careful questioning into the possibility of exposure to chemicals it was discovered that there had been no contact with any of the benzene series or with any gases other than those used routinely and in small amounts for training purposes several months previously. During the summer there had been occasional exposure to the fumes of tetrachlorethane, a non-corrosive decontaminant which is known to be a powerful hepatotoxin but has not been found to produce any significant change in the hematopoietic system.

Physical Examination. On admission the patient's temperature was 101° F. His color was sallow but he was not obviously anemic, nor was there evidence of marked weight loss. He displayed alternately nervous excitement and extreme exhaustion. His eyes were negative externally and no hemorrhages were made out in the optic fundi. There was dried blood in the nares and the nasopharynx showed evidence of marked congestion. The tip of the tongue, buccal mucosæ, and lips presented numerous ecchymotic spots, some measuring nearly 1 cm. in diameter. The gums were normal. The pharynx was dusky red but there was no exudate.

The right tonsillar node was about 1.5 cm. in diameter. There were numerous small, shotty post-cervical nodes on either side. One or 2 small nodes were palpable in the axillæ, and the right epitrochlear node was felt.

The lungs were clear. The heart was normal. Blood pressure 110/70. The abdomen was held tense but there was no spasm, and no masses or tenderness were made out. The liver and spleen were not palpable. The inguinal nodes were small and not impressive. The genitalia were negative. Scattered groups of petechiæ were seen on the lower legs and in the right flank. The deep reflexes were somewhat overactive and equal. There was no edema.

Laboratory Work. (See Table 1.) A Roentgen ray of the chest was negative.

Course. For the first 5 days the temperature showed a daily rise to nearly 101° F., then subsided. During this time the patient's condition remained essentially unaltered, and gross hematuria persisted. Hemorrhagic spots remained in the mouth and a few fresh petechiæ were noted on legs and trunk but there were no further nosebleeds. The patient complained mainly of complete exhaustion and drenching sweats were frequent, but at no time was there any severe prostration or evidence of collapse. Marked postnasal congestion continued to be a troublesome symptom and considerable exudate was obtained on nasal irrigation.

After the 5th day the temperature remained normal and improvement was steady thereafter. By November 2 there was no evidence of bleeding of any kind and the purpuric eruption had practically disappeared. The lymph nodes showed no further enlargement and the spleen was at no time palpable. Convalescence during November and December was marred only by a mild acute enterocolitis and later by an upper respiratory infection with abundant nasal discharge. Occasional herpetiform lesions appeared in the oral mucosa but these were transient, and there was no recurrence of any of the purpuric phenomena.

The patient was discharged symptom-free on Jan. 11, 1943.

Discussion. Despite the absence of significant lymphadenopathy and palpable spleen it is felt that the characteristic lymphocytosis with numerous large lymphocytes and atypical mononuclear forms, combined with a heterophil agglutination of 1:512, establishes the diagnosis of infectious mononucleosis beyond a doubt. The explanation of the associated thrombocytopenia on the other hand is a difficult problem, because in the absence of anemia, leukopenia and sternal marrow changes one can scarcely postulate a depression or dysfunction of the bone marrow. Presumably a combination of vascular

damage as a result of the acute infection, together with loss of circulating platelets at the purpuric sites, is responsible for the widespread hemorrhagic phenomena.[10] The low platelet count in the circulating blood may be an expression of a transient toxic effect exerted peripherally rather than centrally.

It is well known that severe infectious mononucleosis may in its early stages be indistinguishable from acute lymphatic leukemia, and the presence of purpura has long been considered an important diagnostic point in favor of the latter. In the light of the case at hand, however, it is obvious that purpuric and hemorrhagic phenomena with or without thrombocytopenia cannot constitute a valid distinguishing feature between these two conditions. The finding of a well-marked anemia, on the other hand, is exceedingly rare in mononucleosis, and if such a condition appears without obvious explanation, one may well suspect the presence of a leukemic process.

Summary. 1. A case is reported of infectious mononucleosis with associated acute thrombocytopenic purpura.

2. Hemorrhagic skin eruptions, epistaxes, and hematuria are infrequent findings in infectious mononucleosis, but do occur even in the absence of thrombocytopenia.

3. Purpuric phenomena even with marked platelet reduction do not necessarily constitute a significant diagnostic point in favor of leukemia.

REFERENCES

1. Bernstein, A.: Medicine, **19**, 85, 1940.
2. Cottrell, J. E.: Am. J. Med. Sci., **173**, 472, 1927.
3. Downey, H., and McKinlay, C. A.: Arch. Int. Med., **32**, 82, 1923.
4. Longcope, W. T.: Am. J. Med. Sci., **164**, 781, 1922.
5. Magner, W., and Brooks, E. F.: Canad. Med. Assn. J., **47**, 35, 1942.
6. Minot, G. R.: Am. J. Med. Sci., **192**, 445, 1936.
7. Tidy, H. L., and Daniel, E. C.: Lancet, **2**, 9, 1923.
8. Tidy, H. L.: Lancet, **2**, 180, 1934.
9. Tidy, H. L., and Williams, H. J.: Proc. Roy. Soc. Med., **25**, 155, 1931–32.
10. Whitby, L. E. H.: Personal communication.

THE "HEAT RESISTANCE" OF ERYTHROCYTES

A Specific Test for the Recognition of Marchiafava's Anemia*

By Robert Hegglin, M.D.

and

Conrad Maier, M.D.

Zürich, Switzerland

(From the Medical Department of the Medical Faculty of the University of Zürich)

Marchiafava's anemia is a relatively rare clinical entity. Its symptomatology consists chiefly of nocturnal hemoglobinuria, constant hemosiderinuria, pseudomacrocytic anemia with a strong tendency to regeneration of the bone marrow, increased reticulocyte count in the peripheral blood, and leukopenia. In making the differential diagnosis, other forms of hemolytic anemia and hemoglobinuria must be con-

* Translated by Morris Kramer, B.A., M.D.

sidered. As the latter symptom at times retreats almost completely into the background, a lack of nocturnal excretion of hemoglobin does not automatically exclude the disease.

The osmotic resistance test of the erythrocytes allows the demonstration of the presence of spherocytes, and has therefore taken on particular importance in the diagnosis of the constitutional form of hemolytic anemia or hemolytic jaundice. For the diagnosis of Marchiafava's anemia, however, this test is useless, as the fragility of the red cells is not increased. This disease, as the investigations of Ham[1–3] and Hegglin and Maier[4,5] have shown, is due to the action of a hemolysin whose amboceptor is always present in the erythrocytes. In the presence of complement hemolysis takes place. The degree of hemolysis increases as the temperature of the blood rises, and as the pH of the blood falls.

While it is technically rather awkward to test the acid-base balance of the blood, it is on the contrary quite easy to determine the resistance of the red blood cells to increased temperature. The test consists of putting a test tube containing about 5 cc. of blood obtained by means of a dry-air sterilized syringe into the incubator for 6 to 24 hours at a temperature of 37° C. The degree of hemolysis can then be observed with the naked eye.

A quantitative determination of the degree of hemolysis, *i. e.*, the hemoglobin content of the serum, is from a practical standpoint unnecessary. After making the above test in numerous cases of anemia we have, nevertheless, determined the hemolysis according to the method of Wu Hsien.[6]

The results are as follows:

No.	Name	Age (yrs.)	Diagnosis	Serum hemoglobin values at 37° C. After 6 hours (mg. per 100 ml.)	Serum hemoglobin values at 37° C. After 24 hours (mg. per 100 ml.)
1	B. H.	28	Marchiafava's anemia	675	1357
2	S. F.	44	Marchiafava's anemia	570	592
3	G. R.	64	Acquired (?) hemolytic anemia	6	23
4	G. A.	39	Constitutional form of hemolytic anemia (jaundice)	35	180
5	G. L.	27	Constitutional form of hemolytic anemia (jaundice)	33	51
6	H. A.	35	Probably acquired form of hemolytic anemia	14	13
7	K. A.	36	Paroxysmal hemoglobinuria after exposure to cold	11	
8	P. E.	15	Toxic hemolysis (pyrogallic acid)	96	142
	50 normal cases			Hemolysis not increased	
	7 cases of secondary anemia			Hemolysis not increased	
	12 cases of pernicious anemia			Hemolysis not increased	

In Case 7 (paroxysmal hemoglobinuria brought about by exposure to cold), an increase in hemolysis could be observed if immediately after venous puncture the blood was first placed in a refrigerator for 30 minutes, and then brought into the incubator (Donath-Landsteiner).

In Case 8 (toxic hemolysis through external application of pyrogallic acid), distinct hemolysis was already evident on taking the blood out of the vein. This, however, did not increase on being further warmed in the incubator.

In pernicious anemia, if the blood remains in the incubator for 48 hours at 37° C., one may at times observe a slight hemolysis. However, this never attains a value over 150 mg. per ml.

It is evident from the above table that the blood in Marchiafava's anemia tends to hemolyse on application of warmth. It should also be mentioned that the hemolysis increases greatly when the blood is shaken from time to time while in the incubator. From the incidental degree of hemolysis *in vitro*, however, it is impossible to draw conclusions regarding the possible phase or stage of the disease.

Summary. The concept of the "*heat resistance*" of erythrocytes is herewith presented. If hemolysis of clotted blood *in vitro* is evident to the naked eye after 6 hours at 37° C., it appears to be pathognomonic, specific evidence of the presence of Marchiafava's anemia.

REFERENCES

1. Ham, T.: Arch. Int. Med., **64**, 1271, 1939.
2. Ham, T., and Castle, W. B.: J. Clin. Invest., **19**, 788, 1940.
3. Ham, T., and Dingle, J.: J. Clin. Invest., **18**, 657, 1939.
4. Hegglin, R., and Maier, C.: Klin. Wchnschr., **2**, 956, 1941.
5. Hegglin, R., and Maier, C.: Ergebn. d. inn. Med., vol. **63**, 1943.
6. Wu Hsien: J. Biochem., **2**, 189, 1923.

HOMOLOGOUS SERUM JAUNDICE*

A Review of the Literature and Report of a Case

By Lieut. John R. Neefe, M.C., A.U.S.

T. Grier Miller, M.D.

and

Francis W. Chornock, Ph.D.

Hospital of the Univ. of Penna.
Philadelphia, Pa.

(From the Gastro-Intestinal Section [Kinsey-Thomas Foundation] of the Medical Clinic)

A possible hazard involved in the clinical use of biologic preparations containing homologous blood products is suggested by the recent reports of cases of jaundice following their parenteral administration. The importance of this problem is well illustrated by the 1942 outbreak of hepatocellular jaundice in the United States Army. This outbreak was observed to follow by a more or less fixed time interval the parenteral injection of certain lots of yellow fever vaccine, and although the exact etiology has not yet been determined, it seems to have been related to the human serum component of that vaccine.

* This investigation was aided in part by the Commission on Measles and Mumps, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of The Surgeon-General, A. U. S.

However, in large bodies of men living in crowded or otherwise abnormal conditions, it is difficult to exclude the possibility of transmission by some other means, and for this reason, the study of an isolated case in civil life may be of value in the further analysis of this problem. We have been led, therefore, to report the case of a physician who developed severe and prolonged hepatocellular jaundice 11 weeks after the intravenous injection of a pooled mumps convalescent plasma.

Review of Literature. *Incidence.* The important data on the major outbreaks of jaundice that have been reported as occurring in relation to the administration of biologic products containing homologous blood factors are tabulated below. One notes that the disease has been associated with the use of glycerinated humanized smallpox lymph,[18] yellow fever vaccine,[3,8,9,13] measles convalescent serum,[21] pooled mumps convalescent serum,[21] whole blood transfusions,[21] pooled and dried reconstituted human adult serum,[23] and pappataci fever vaccine.[27] Analogous cases have been reported after immunizing procedures involving the use of homologous sera in horses.[4,29]

Etiology. Since the other components of the biologic products have seemed to be eliminated as factors in the production of the disease process, the injected blood, plasma or serum naturally has been suspected of carrying the icterogenic agent. Indeed, that human blood and some of its derivatives may contain a transmissible icterogenic agent has been demonstrated by Oliphant and his associates,[25] who were able to transmit the disease to human volunteers by the subcutaneous injection of serum obtained from patients in the preicteric or icteric stages of postyellow fever inoculation jaundice. Cameron[2] and Voegt[31] also have succeeded in producing jaundice in volunteers by subcutaneous or intramuscular injection of serum or blood from patients with infective hepatitis. Findlay and Martin,[11] by introducing the nasal washings of patients with postyellow fever inoculation jaundice into the nasopharynx of volunteers and observing the subsequent occurrence of jaundice in a significant number, demonstrated that the agent may be present in the nasopharynx. All attempts to transmit the disease to animals have thus far been unsuccessful.[2,25]

Extensive studies of these icterogenic blood products, however, have failed to reveal the exact nature of the causative agent; and yet certain properties, including its transmissibility in serum, its lack of visibility under the microscope, its passage through bacteria-retaining filters, its persistence in serum-chick embryo media and its resistance to various procedures which ordinarily kill vegetative bacteria have led to the belief that it may be a virus. At present, this concept cannot be denied or confirmed.

The clinical and pathologic pictures of this disease and those of infective hepatitis* are so similar that some feel they are identical and due to the same causative agent. Others, however, believe that different etiologic agents are concerned. The various opinions are summarized in a recent *Lancet* editorial[7] which suggests three possibili-

* The term infective hepatitis, as used here, is synonymous with catarrhal jaundice, infectious hepatic jaundice and epidemic jaundice or hepatitis.

TABLE 1.—STATISTICAL DATA ON SOME REPORTED GROUPS OF CASES OF HOMOLOGOUS SERUM JAUNDICE*

Source of report (date)	Location	Suspected source of icterogenic agent	Number of subjects injected	Number of cases of jaundice	Incidence of jaundice (%)	Number of deaths	Incubation period (weeks)	Duration of jaundice (weeks)
Lurman,[18] 1885	Bremen	Glycerinated humanized lymph (smallpox vaccine)	1,289	191	14.8	....	4 to 28	
Findlay *et al.*,[9] 1939	Varied	Yellow fever vaccine	2,200	48	2.2	....	8 to 32	
Circ. Letter 95, Surg.-Gen. Office.[3]	U. S. Army	Yellow fever vaccine	....	28,585	....	62	10 to 13 (average)	4 to 8 (average)
Fox, Manso, Penna and Para,[13] 1942	Brazil	Yellow fever vaccine	....	....	....	....	12 to 20 (average)	5 to 24
		Lot No. 489	9,604	736	7.7	25		
		Lot No. 494	9,587	150	1.5	(from Nos.	2 to 78	
		Other lots	87,987	93	0.1	489 and 494)	(extremes)	
Sergiev,[27] 1940	....	Pappataci fever vaccine	360±	109	30.0	....	9 to 21	
Mem. M. O. Min. of Health,[21] 1943	England	Pooled measles convalescent serum (K-60)	109	37	37.6	8	2 to 16	
		Measles adult serum (No. 488)	....	11	....	1	11 to 23	
		Pooled mumps convalescent serum	266	86	32.3			
	A.R.C. Harvard Unit	Mumps convalescent serum	....	48	....	....	5 to 19	
Morgan and Williamson,[23] 1943	England	Reconstituted dried serum; pooled plasma	56	9	16.1	....	7 to 16	
Beeson,[1] 1943	Grady Hospital, Ga.	Blood or plasma transfusions	....	7	....	....	4 to 29	
Oliphant *et al.*,[25] 1943	Virgin Islands	Yellow fever vaccine	1,039	153	14.7	0	10 to 19	1 (average)
	Experimental inoculation volunteers	Yellow fever vaccine and pooled serum from patients jaundiced after yellow fever vaccine	189	30	15.8	0	4 to 19	1 to 7
Cameron,[2] 1943	Experimental inoculation volunteers	Blood or serum from patients with infective hepatitis	7	6	86.0	0	4 to 24	

* The statistics for certain groups are incomplete as the table includes only those appearing in the literature to date.

ties, namely, that the two diseases are caused by: (1) the same virus, (2) different strains of the same virus, or (3) different agents producing the same clinical picture.

In support of the proposition that the infective hepatitis virus is at least one of the causes of serum jaundice is the recent report of Cameron[2] concerning the development of jaundice in volunteers inoculated with blood or serum from patients with infective hepatitis. His cases represented serum jaundice in which the icterogenic agent was almost certainly that of infective hepatitis, and, furthermore, the interval between the inoculation and the onset of the disease was as long as 6 months, suggesting that the difference in the length of the incubation period of the two diseases does not necessarily indicate different etiologic agents. Against the hypothesis of the infective hepatitis virus as the only cause of serum jaundice is the apparent absence of contact infection. This was observed as a striking feature of the United States Army outbreak related to yellow fever vaccine.[3]

As in other diseases, individual susceptibility or predisposition appears to play an important rôle. Some investigators[2,9,13] are of the opinion that manifestations of the disease may occur only after some other factor has rendered the individual susceptible. Cameron[2] feels that the onset may be delayed until general resistance is lowered, for example, by conditions (fatigue, malnutrition, exposure, etc.) such as occur among the men of an army in the field. Thus his volunteers did not develop jaundice until they had spent some time on active field service.

Pathologic Anatomy. Dible and his associates[6] have studied the hepatic pathologic changes in 56 cases of non-fatal acute hepatitis, the specimens being obtained by aspiration biopsy. The group was composed of 14 cases of epidemic hepatitis, 5 cases of jaundice following the injection of mumps convalescent serum (American Red Cross Harvard Unit group), 2 cases of jaundice following the transfusion of serum and 35 cases of arsenotherapy jaundice. A hepatic inflammation of varying intensity and distribution was common to all and, regardless of the etiology, one type of case could not be differentiated from another by histologic criteria. The essential changes consisted of hepatic cell necrosis and autolysis, associated with leukocytic and histiocytic infiltration. The centers of the lobules showed the first of these changes to the most marked degree, and the portal tracts the greatest cellular infiltration. In cases mild from the beginning, or in which the lesion was retrogressing, the periportal cell accumulations predominated, in contradistinction to the more severe cases in which hepatic cell degeneration was more pronounced and the leukocytic and histiocytic infiltration more widespread. Some cases exhibited nodular hyperplasia and cirrhotic changes. As a rule, diffuse hepatitis was found to heal completely and rapidly, though in cases running a longer course, residual fibrosis persisted in the portal zones even after apparent clinical cure. The mechanism of the production of icterus was thought to be due to the disruption of the liver-cell columns and their intercellular bile canaliculi, the functional inadequacy of the

damaged cells and the plugging of the canaliculi with bile thrombi. There was no evidence of bile stasis in the interlobular branches of the bile ducts, further confirming the intralobular nature of any obstruction to the outflow of bile that existed.

The main hepatic changes in the fatal cases of jaundice following yellow fever vaccination in the United States Army were those of acute or subacute yellow or red atrophy.[3] The investigators of the cases that occurred in Brazil[13] reported similar observations, occasionally finding, however, the changes of infective biliary cirrhosis. Other abnormalities in the United States Army cases included marked edema and intense inflammation of the gastro-intestinal tract, usually most pronounced in the cecum, bile nephrosis, acute or subacute splenic tumor and hemorrhages in various locations.

Clinical Features.[3,9,13,21,25] The incubation period or interval between the injection of the suspected product and the development of jaundice is regarded as one of the most important distinguishing features of this disease and is usually quite long, varying from 2 to 32 weeks, the average being 8 to 12 weeks. The onset may be asymptomatic or with a "grippe-like" syndrome similar to that of infective hepatitis. During the preicteric period, polymorphic rashes, urticaria and joint pains are common and have been emphasized by some as especially characteristic of this type of hepatitis. Abdominal pain may be present and occasionally may simulate closely that of acute appendicitis. Anorexia, nausea and vomiting are frequent and either diarrhea or constipation may be present. The temperature is often normal or only slightly elevated. Jaundice gradually appears in most cases and the course thereafter is similar to that of infective hepatitis. Worthy of mention is the fact that some authorities are convinced that the disease may occur without icterus. Severe cases, such as occurred in one outbreak in England due to measles serum, may exhibit irritability, restlessness, intractability, delirium, screaming, extensor plantar reflexes, hematemesis and bloody stools. Pruritus may be severe and may occur in the preicteric period.

The physical observations are also similar to those of infective hepatitis. Dehydration is often marked. The liver may be enlarged and tender, but in the less severe cases is often not palpable. The spleen is often palpable during some stage of the illness.

Laboratory Observations.[3,13,21,25] If the disease is severe or of long duration, anemia may occur. The leukocyte count is usually normal, though leukopenia is not uncommon. The differential count occasionally reveals an increase in monocytes. Greenblatt and Kaplan[14] recently reported the presence of an unusually high percentage of "target cells," a variant of red blood corpuscles, in the circulating blood of 22 patients with postyellow fever inoculation jaundice. They are characterized by a small central mass of hemoglobin surrounded by a clear area, which in turn is circumscribed by an additional ring of hemoglobin; such cells are said to be more resistant than normal to hemolysis by hypotonic saline solution. They, however, are also found in other conditions and thus are not specific for serum jaundice.

The urine usually contains bilirubin and urobilinogen, and bile salts may be present. The stools may be acholic for variable periods. The serum bilirubin and icterus index are of course elevated. Liver function tests show varying degrees of disturbance of hepatic function. The histamine test may be positive in the preicteric period.[2]

Prognosis. Recovery in 4 to 8 weeks was the rule in the United States Army cases[3] and, in most instances, was complete. In a few, persistent liver damage apparently resulted. The mortality was approximately 0.2%. The highest mortality reported was in one of the civilian groups in England ascribed to measles serum, 8 deaths occurring among 37 cases.[21]

Prophylaxis. The only prophylactic measure thus far recommended has been the rejection of potential blood donors who give a history of recent non-surgical jaundice.[1,10] It would also seem advisable to report all cases of serum jaundice to an appropriate authority so that the cause may be investigated and further therapeutic use of the suspected product prevented.

Case Report. A male physician, 43 years of age, developed, in August 1942, an attack of jaundice that persisted in an intense form for more than 3 months. The initial diagnosis was infective hepatitis, and not until the severity of the process necessitated a complete revaluation of the case was the significance of the preceding history fully appreciated.

History. The past medical history contained one important item, a 3 weeks illness in 1933 characterized by fever as high as 102° F., marked jaundice and some hepatic enlargement. It was regarded as a typical case of catarrhal jaundice ("infective hepatitis"). He was then in good health until June 1942, when he contracted mumps from one of his children. During this illness he developed considerable anorexia, nausea, epigastric discomfort and tenderness, suggesting the possibility of a complicating pancreatitis, and 200 ml. of pooled mumps human convalescent plasma were therefore administered intravenously. He recovered promptly and was again in good health until mid-August 1942, when after 2 to 3 days of vague epigastric discomfort scleral icterus was first noted (approximately 11 weeks after the injection of the plasma). The intensity of the jaundice progressively increased, and on the 40th day of his illness, because of anorexia, dehydration, weight loss and general discomfort, he was admitted to the University Hospital for more vigorous treatment and study.

The jaundice reached its maximum on the 43rd day. Anorexia was marked, pruritus severe, mental depression constant, and he had lost 30 pounds in weight. Symptomatic and objective improvement then began and, except for a temporary relapse between the 52nd and 63rd days, was progressive. Visible jaundice persisted, however, until between the 90th and 117th days, during which interval he was not under observation. His pruritus also disappeared during that period and he regained his normal weight level. Subsequently he was permitted gradually to resume his normal activities and he has since been in good health.

Physical Observations. When first seen, early in the disease, physical examination was entirely negative except for the obvious jaundice. The liver, however, soon became palpable and slightly tender and during the mid-stage of the disease, its edge was palpable as far down as the level of the umbilicus (6 cm. below the costal margin). Though more firm than normal, it then became gradually smaller but was still vaguely palpable on the 117th day. Between the 32nd and 34th days the spleen was just palpable, but was never felt thereafter. The skin was exceedingly dry and the site of numerous excoriations until the late phase of the illness; it then gradually assumed a

more normal character and the excoriations healed rapidly. Bradycardia was a constant feature, and the temperature was never elevated.

Special Examinations and Studies. Blood studies showed nothing unusual except a gradual drop in the hemoglobin level to 10.1 gm. (52nd day). Leukocyte and differential counts were not abnormal.

The urine was deeply colored from the onset, and the first examination revealed urobilin, bilirubin and bile salts. The latter disappeared (Hay's and Oliver's tests) about the 50th day, though the serum bilirubin 2 days later was 22 mg. per 100 ml. of blood. Bilirubinuria was not demonstrable after the 85th day (serum bilirubin, 6.4 mg. per 100 ml.). Routine urinalyses were otherwise consistently negative. During the mid-stage of the disease, a urea clearance test showed no significant abnormality of renal function. The blood urea nitrogen values were always normal.

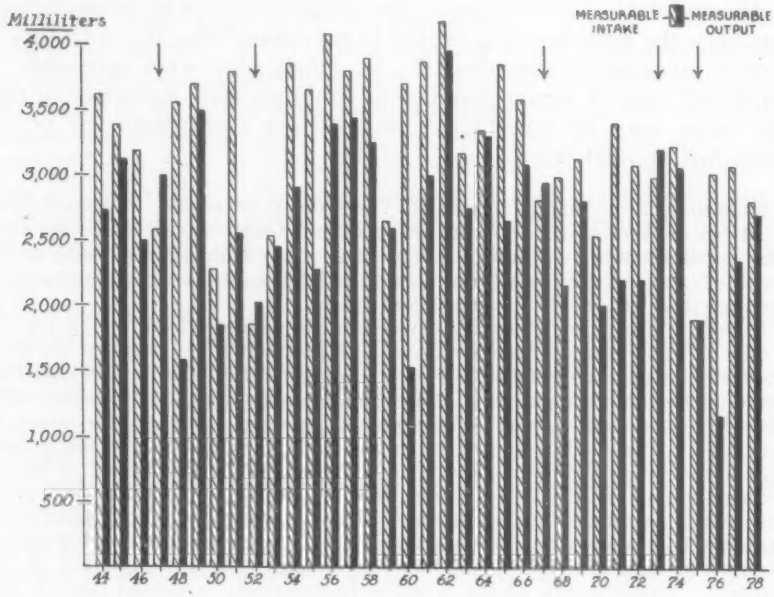


CHART 1.—Measurable intake and output of fluid during 44th to 78th day of the disease. Previously an oliguria had been present. Arrows indicate days on which output equaled or exceeded intake; abscissæ, days of disease.

The stools were light in color or truly acholic from the onset of the jaundice until the 46th day, after which the bile content steadily increased.

A disturbance of water balance was observed. During the early stage of the disease, quantitative measurement of the intake and output of fluids was not possible, but the patient stated that a very definite oliguria occurred. By the time the jaundice had reached its height (43rd day), however, a pronounced diuretic tendency was noted (Chart 1), and this persisted until the time of the patient's discharge from the hospital (83rd day).

The serum bilirubin level, as determined by the method of Malloy and Evelyn,[19] rose progressively until the 43rd day, when a value of 41.6 mg. per 100 ml. was obtained (Chart 2). The level then gradually dropped to 22 mg. (52nd day). At that time a temporary relapse occurred, with an aggravation of all the symptoms, and the serum bilirubin persisted at about 22 mg. until the 64th day, after which it again gradually fell. On the 117th day, the level was still slightly elevated (1.9 mg.). When again checked 3 months later, its concentration was normal.

Studies of the blood cholesterol and its ester fraction (Chart 2) yielded results compatible with those usually found in hepatocellular jaundice. The concentration of the total cholesterol was low normal during the early stage of the disease, while that of its ester fraction was below normal. Both gradually increased with the fall in the serum bilirubin level and general clinical improvement, the value of the total actually rising to high normal toward the termination of the disease. The last ester fraction value shown on the chart, which is low, is unexplained, but may have been due to a technical error since the concentration was normal when checked a few weeks later.

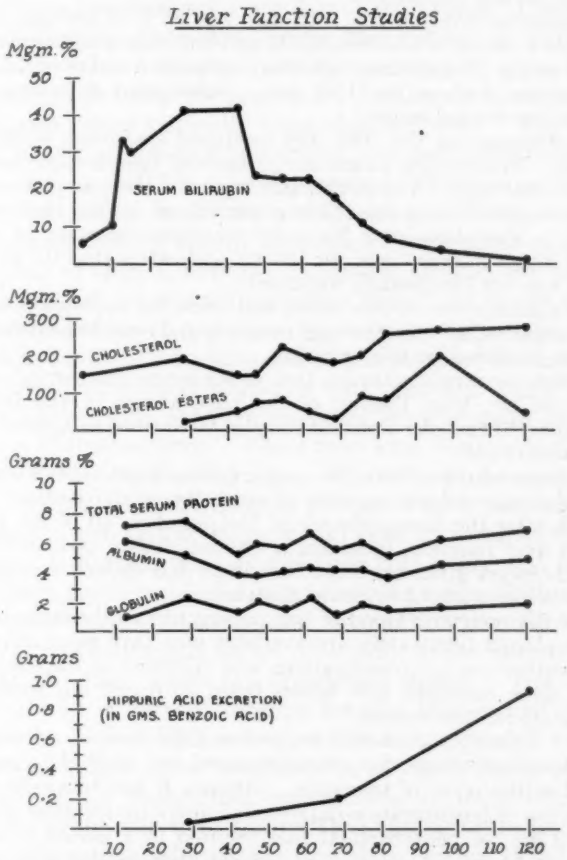


CHART 2.—Data on the serum bilirubin, cholesterol and protein concentration in the blood serum and on the results of the hippuric acid excretion tests. Abscissæ indicate days of disease.

Serum protein studies (Chart 2) were frequently made and the total protein values were not unusual. Likewise, the serum albumin values, except for a surprisingly high concentration (6.1 gm. per 100 ml.) on the 12th day of jaundice when the initial determination was made, were not unusual, the level gradually falling to a minimum of 3.9 gm. per 100 ml. during the mid-stage of the disease. The globulin level, however, in spite of the duration and severity of the illness, was usually low or low normal, the average of 12 determinations being 1.7 gm. per 100 ml., with 6 determinations below this level.

Hippuric acid tests of liver function (intravenous) were done on three occasions (Chart 2). The first, on the 28th day, revealed a marked impairment of this function, practically no hippuric acid being excreted during the 1st hour. The result obtained may have been abnormally low because the volume of urine excreted was small. However, even when the 2nd hour excretion was added to the 1st, the total was much less than that normally eliminated in 1 hour. Related to this first examination was an intense and prolonged flush, most disagreeable to the patient, following the injection of the sodium benzoate. This reaction was much less intense with the second test, when the liver function had improved, and was entirely absent with the third, when the test indicated normal function.

The prothrombin level on the 13th day was 65% of normal, and on the 65th day, after a period of oral vitamin K and bile salts administration, 100%.

A test for serum phosphatase (alkaline) revealed a value of 12 Shinowara units (top normal 8.6) on the 15th day. Subsequent determinations gave results within the normal range.

Duodenal drainage on the 10th day produced specimens containing only traces of bile. Microscopic examination showed innumerable mononuclear cells of an unusual type. The pathologist regarded them as plasma cells.

The blood vitamin C level was 0.38 mg. per 100 ml. on the 43rd day (normal 0.4 to 1 mg.). Five days after the daily oral administration of 500 mg. of ascorbic acid, the level was 1 mg. per 100 ml., indicating that the absorption of this vitamin was not significantly impaired.

Dark-field examinations of the blood and urine for *Leptospira icterohæmorrhagiæ* were negative, as were the agglutination and complement-fixation tests for antibodies produced by this organism.

A yellow fever virus neutralization test on the serum was carried out through the courtesy of Dr. Max Theiler, of the Laboratories of the International Health Division, Rockefeller Foundation, and no antibodies against the yellow fever virus were found.

Roentgenologic examination of the upper gastro-intestinal tract early in the disease revealed only delayed motility through the small intestine.

One month after the disappearance of the jaundice, all of the above tests pertaining to liver function, including a bromsulphalein test, yielded normal results. A cholecystogram has since been done and showed a normally functioning gall bladder without evidence of stones.

Samples of the preicteric blood of our patient and of the suspected mumps convalescent plasma fortunately are available and have been turned over to appropriate authorities for investigations with reference to the etiologic agent. Injection of these materials into horses failed to reveal any evidence of an agent icterogenic for this animal.*

Treatment. Therapy varied with the course of the disease. A low-fat, high-protein, high-carbohydrate diet, supplemented by multiple vitamins, was administered to the point of tolerance. Vitamin K and bile salts were given orally. The use of barbiturate sedatives was discontinued after the administration of 0.2 gm. of pentobarbital had resulted in a period of somnolence lasting over 24 hours. A mixture of chloral hydrate and sodium bromide was found to be the most satisfactory sedative for this patient. From the 43rd to the 65th day, in spite of what was regarded as an adequate fluid intake by mouth and chiefly because of its reported value in liver disease, an intravenous glucose solution was administered daily, and during the early part of that period, marked improvement, as indicated by a fall in the level of serum bilirubin, occurred. A temporary relapse between the 52nd and the 63rd days led to the use of choline chloride, 1.5 gm. daily by mouth, and whether initiated by this drug or not, progressive improvement was promptly resumed.

* This work was carried out by Major T. C. Jones, V.C., and Captain Fred D. Maurer, V.C., at the Veterinary Research Laboratory, Army Remount Depot, Front Royal, Va., through the courtesy of Brigadier General Raymond A. Kelser.

Discussion. The differential diagnosis in this case involved the usual question of ordinary catarrhal jaundice (infective hepatitis) *versus* homologous serum jaundice. The fact that the patient had suffered a typical attack of catarrhal jaundice 10 years prior to the recent illness is worthy of note in relation to this problem. A survey of the medical textbooks and recent literature suggests that the occurrence of two separate attacks (not relapses) of infective hepatitis in the same individual is probably uncommon, although Ford[12] records several instances and Lucké[17] has encountered a number of such cases. Cameron, however, states that in Palestine, where the disease is endemic, most authorities agree that one attack confers a permanent type of immunity and that second attacks are unusual. Furthermore, in our patient, the two illnesses were clinically somewhat different. The first began with the typical "grippe-like" prodrome and was associated with fever ranging as high as 102° F. In the second, icterus was the first significant manifestation, no prodromal symptoms having occurred, and fever was conspicuously absent throughout the course of the disease.

On the basis of these differences in clinical picture, the history of an injection of pooled mumps convalescent plasma 11 weeks prior to the onset and the absence of any other satisfactory explanation, the diagnosis of homologous serum jaundice seems justified in this case.

The mumps convalescent plasma was obtained from a group of 13 white soldiers, who were convalescing from mumps at one of the army camps in this country. These men were bled in April 1942, and the plasma was pooled and frozen. An attempt has been made to trace these donors, for knowledge of the previous or subsequent occurrence of jaundice in any of them would tend to confirm the diagnosis in our case. Unfortunately, by the time this study was initiated, all but 1 had been transferred to distant theaters and reliable information regarding their medical histories and vaccination records could not be obtained. It was learned, however, that none of the donors had visible jaundice at the time when the blood was drawn. The vaccination records would have been of interest because of the high incidence of jaundice in the United States Army at that time related to the use of certain lots of yellow fever vaccine. It is theoretically possible that one or more of the donors had received one of these icterogenic lots and that the agent was then transmitted through him to our patient. Lacking confirmatory information, the above conception is merely an intriguing hypothesis. Accordingly, this case probably should be regarded, for the time being, as belonging to the group of cases that have been reported as following the use of mumps convalescent serum. In this connection, the fact that the disease has occurred in patients given this type of serum prophylactically indicates that a preceding mumps infection is not necessary for the subsequent development of jaundice.

In view of the data in the literature on water balance in hepatic disorders, it is interesting that in our patient, during a certain stage of the disease, the urinary output, in comparison with the intake of fluid, was high.

Molitor and Pick[22] were among the first to show that water by mouth in the Eck fistula dog resulted in a greater blood dilution and a more prompt diuresis than in the normal. A greater total urinary excretion was also noted. These observations have been confirmed by others and this led Crandall and Roberts[5] to suggest that the increased water exchange is due to a suppression of liver function. Steigmann *et al.*,[28] on the other hand, noting the occurrence of oliguria during the acute stage of hepatic disease, believe that liver damage results in water retention by the tissues and that diuresis is a secondary manifestation indicative of beginning recovery. In our patient, an initial water retention occurred, as manifested by oliguria in spite of an adequate fluid intake; this was followed by a diuresis lasting throughout the period of hospitalization (40 days). The early water retention is in accord with the explanation of Steigmann and his group. The period of diuresis, which occurred without relation to intravenous glucose administration, was, however, much too prolonged to represent merely the excretion of retained tissue fluid and, in this case, could hardly be regarded as a favorable prognostic sign.

Diuresis, therefore, no matter how it may eventually be interpreted or explained, seems to be a manifestation of a certain stage of hepatocellular disease, and may possibly be related to prolonged suppression of liver function.

A review of the recent literature[15,16,20,24,26,30] pertaining to the fractionation of serum proteins in jaundice suggests that the tendency to low-globulin levels, as found in this case, is unusual. Tumen and Bockus[30] did note the occurrence of low-globulin levels in some cases of acute hepatocellular damage, but no mention was made of this observation in cases of prolonged jaundice. Future cases of serum jaundice, therefore, should probably be studied in this respect in order to determine if this tendency is characteristic of the disease.

The level of serum bilirubin varied inversely and the total cholesterol and cholesterol esters directly with the clinical condition of the patient. This association has been previously observed.[16b]

Pruritus ceased about the 90th day, 40 days after the disappearance of bile salts from the urine, as determined by the methods of Hay and Oliver, but only 5 days after the cessation of bilirubinuria. One wonders about the significance of this relationship in reference to the etiology of pruritus, realizing that the methods used for the detection of bile salts in the urine are not entirely reliable.

The institution of daily intravenous glucose therapy was followed by a decrease in the level of serum bilirubin, an interruption in the steady loss of weight, and a slight increase in the total serum protein. While this improvement may have been incidental, the observations at least suggest that this form of therapy may have been beneficial.

Administration of a homologous blood product probably has been frequently overlooked as an explanation of some cases of obscure jaundice. The duration of the interval between the injection and the resultant jaundice, which is months rather than weeks, doubtless has accounted for the failure to associate the cause and its effect. In an

attempt to find such a relationship, we have found among our records 2 additional cases in point. One occurred in a syphilitic colored woman of 38 years, who developed an afebrile attack of jaundice, with hepatomegaly, that lasted 4 weeks. Her history revealed the administration of 3 blood transfusions for anemia that developed during malarial fever therapy, these having been given 6 to 7 weeks before the onset of jaundice. This patient had also received blood from 2 different malarial blood donors 3 to 4 months before the development of hepatitis, which brings up the possibility of the transfer of an icterogenic agent with therapeutic malarial blood inoculations. The other patient, a 22 year old white woman, had been given 4 blood transfusions for anemia, and 82 days later developed jaundice, hepatomegaly, and slight fever. Beeson[1] and others have regarded similar cases as due to an agent in the injected blood. At present, however, such a case can be differentiated from infective hepatitis only by the interval of 1 to 3 months that usually elapses between the injection and the onset of jaundice.

Summary. 1. A case of severe and prolonged hepatocellular jaundice that followed the injection of pooled mumps convalescent plasma is reported and represents a typical example of a problem that occasionally may be encountered as a result of the increasing use of human blood and its derivatives in modern therapeutics. The question of similar hepatocellular jaundice without administration of homologous blood has not been considered in this report.

2. The features of homologous serum jaundice as reported in the literature are reviewed.

REFERENCES

1. Beeson, P. B.: J. Am. Med. Assn., **121**, 1332, 1943.
2. Cameron, J. D. S.: Quart. J. Med., **12**, 139, 1943.
3. Circular Letter No. 95, Office of the Surgeon-General: J. Am. Med. Assn., **120**, 51, 1942; Mil. Surgeon, **91**, 386, 1942.
4. Cox, H. R., Phillip, C. B., Marsh, H., and Kilpatrick, J. W.: J. Am. Vet. Med. Assn., **93**, 225, 1938.
5. Crandall, L. A., and Roberts, G. M.: Am. J. Physiol., **117**, 318, 1936.
6. Dible, J. H., McMichael, J., and Sherlock, S. P. V.: Lancet, **245**, 402, 1943.
7. Editorial: Lancet, **244**, 683, 1943.
8. Editorial: J. Am. Med. Assn., **119**, 1110, 1942.
9. Findlay, G. M., and MacCallum, F. O.: Tr. Roy. Soc. Trop. Med. and Hyg., **31**, 297, 1937.
10. Findlay, G. M., MacCallum, F. O., and Murgatroyd, F.: Tr. Roy. Soc. Trop. Med. and Hyg., **32**, 575, 1939.
11. Findlay, G. M., and Martin, N. H.: Lancet, **244**, 678, 1943.
12. Ford, J. C.: Lancet, **244**, 675, 1943.
13. Fox, J. P., Manso, C., Penna, H. A., and Para, M.: Am. J. Hyg., **36**, 68, 1942.
14. Greenblatt, I. J., and Kaplan, G.: J. Am. Med. Assn., **122**, 806, 1943.
15. Israel, H. L., and Reinhold, J. G.: J. Lab. and Clin. Med., **23**, 588, 1938.
16. Lichtman, S. S.: Diseases of the Liver, Gallbladder and Bile Ducts, Philadelphia, Lea & Febiger, pp. 232 and 326, 1942.
17. Lucké, Balduin: Personal communication.
18. Lurman: Berl. klin. Wchnschr., **22**, 20, 1885.
19. Malloy, H. T., and Evelyn, K. O.: J. Biol. Chem., **119**, 481, 1939.
20. Miller, T. G., and Machella, T. E.: Nelson's Loose-leaf Medicine, **5**, 486, 1940.
21. Ministry of Health, Memorandum prepared by Medical Officers of the, Lancet, **246**, 83, 1943.
22. Molitor, H., and Pick, E. P.: Arch. exper. Path. u. Pharmakol., **97**, 317, 1923.
23. Morgan, H. V., and Williamson, D. A. J.: Brit. Med. J., **1**, 750, 1943.

24. Myers, W. K., and Keefer, C. S.: Arch. Int. Med., **55**, 349, 1935.
25. Oliphant, J. W., Gilliam, A. G., and Larson, C. L.: Pub. Health Rep., **58**, 1233, 1943.
26. Peters, J. P., and Eisenman, A. J.: Am. J. Med. Sci., **186**, 808, 1933.
27. Sergiev, P. G., *et al.*: Ter. Arkh., **18**, 595, 1940. (Cited by Oliphant *et al.*, Ref. 25.)
28. Steigmann, F., Popper, H., and Meyer, K. A.: J. Am. Med. Assn., **122**, 279, 1943.
29. Theiler, A.: 5th and 6th reports of the Dir. of Vet. Res., Union of S. Africa, Dept. of Agr., p. 7, 1918.
30. Tumen, H., and Bockus, H. L.: Am. J. Med. Sci., **193**, 788, 1937.
31. Voegt, H.: München. med. Wchnschr., **89**, 76, 1942.

BLOOD STUDIES IN ALLERGY

II. The Presence in Allergic Disease of Atypical Lymphocytes and Symptoms Suggesting the Recovery Phase of Infectious Mononucleosis*

By Theron G. Randolph, M.D.

and

Elizabeth Barber Gibson

Ann Arbor, Mich.

(From the Allergy Clinic, Department of Internal Medicine, University of Michigan Medical School.)

In performing differential white cell counts in patients with allergic disease, one of us (E.B.G.) noted the frequent occurrence of large mononuclear cells indistinguishable from the atypical lymphocytes seen in infectious mononucleosis. The number of such cells was comparable to the blood findings in the subsiding phase of infectious mononucleosis, but distinctly less than that observed in the active stage of this disease.

We then observed that several patients under study for allergic disorders had previously been suspected of having infectious mononucleosis. The finding of atypical lymphocytes had aroused this suspicion in the majority of instances. In others, the general symptoms of debility or the presence of a cervical adenopathy had suggested the diagnosis. It is of interest that both allergic disease and infectious mononucleosis commonly occur during early adult life in patients otherwise in the best of health.

Weakness, lassitude, headache, or general malaise are often the outstanding symptoms in infectious mononucleosis. Not infrequently the weakness and related symptoms may persist for many months following the acute stage of the disease. Although these symptoms are well recognized as part of the clinical picture of infectious mononucleosis, their presence in clinical allergy has not been sufficiently emphasized. Rowe[13,14] in 1929 described "allergic toxemia" resulting from long-standing food allergy. According to him, "This toxemia produces drowsiness, mental confusion, slowness of thought, difficulty in remembering and concentrating, lack of initiative and ambi-

* This study was financed in part by the Parke, Davis Company.

tion, irritability, despondency, fatigue, weakness, bodily aching, and a feeling of 'being poisoned'." He found these symptoms more frequently in women than in men and noted their prompt disappearance after dietary management. Vaughan[16] mentioned the "droopy, loggy, no 'count feeling" resulting from the ingestion of an allergenic food. Similar symptoms in patients with food allergy manifestations have been observed by others.[3,12]

The present study deals with a series of 24 allergy patients having fatigue or weakness as a major complaint. The fatigue in these cases was unrelieved by rest, even though more than an average amount of sleep was obtained nightly. Some patients complained of being more tired in the morning than when they had gone to bed in spite of receiving 10 to 12 hours of sleep. The characteristic drowsiness and inertia were particularly troublesome during the first few morning hours, but sometimes persisted throughout the day and not uncommonly were present daily for weeks or months. In some cases, drowsiness to the point of sleepiness was more prominent 1 to 2 hours after a meal containing allergenic foods. Certain students, at the time of allergic symptoms, found it difficult to remain interested and attentive during the school day, and during the evening were overcome by a compelling sense of fatigue and sleepiness. "Fuzzy thinking" and the inability to concentrate and to remember details proved a distinct handicap in certain instances. Some patients complained of being "dragged out" and lethargic to a degree that it required a distinct effort to carry out their ordinary daily routine. Others had generalized aching, apparently similar to the deep aching sensation associated with the rapidly dropping leukocyte count in the early stages of agranulocytosis due to drug allergy.

Such symptoms often appeared in association with allergic rhinitis, bronchial asthma or some other easily identified allergic manifestations; but when occurring in connection with some less readily recognized allergic expressions, such as the migraine type of headache or certain gastro-intestinal symptoms, the underlying allergic mechanism was frequently not appreciated. This was particularly true when the fatigue or lassitude represented the major complaint at the time the patient was seen, although the past history may have been replete with evidence of allergic disease. A history including details of all probable allergic manifestations occurring from infancy on, including "well focused" questions regarding the major food, drug, and inhalant allergens, will serve to detect many of these cases.

The fatigue, drowsiness, and related symptoms in this series of patients appeared most commonly as the result of allergic intolerance to foods, our experience in this respect confirming the earlier observation of Rowe. Such symptoms have been observed repeatedly after the trial ingestion of foods in susceptible patients, occurring both in association with, and not infrequently in the absence of, other evidence of allergic intolerance.

In the series studied, each patient had at least one clinical allergic manifestation in addition to his complaint of fatigue. As may be

TABLE 1.—ATYPICAL LYMPHOCYTES IN 24 ALLERGIC PATIENTS

Case	Age	Sex	Diagnosis (see key)*	Propylene glycol stain				Differential count, Wright stained film (%)							Downey's classif. atypical lymphs.	Heterophil antibody				
				Total white blood count (thous./c.mm.)	Differential count in counting chamber (%)			Neutrophils	Eos.	Bas.	Normal lymph.	Atypical lymph.	Monocytes	Smudges		1/4	1/8	1/16	1/32	1/64
					Neutrophils	Eos.	Mononuclears													
R. P.	29	M	4, 5	5.6	55	5	40	52.0	5.5	0.5	14.5	17.5	1.5	8.5	III	+++	++	+	+	0
D. J.	23	F	1, 2, 3, 5	7.1	64	1	35	59.0	3.0	0.5	18.5	9.0	3.0	7.0	III	+++	++	±	0	
E. D.	36	F	2, 5, 6	8.3	58	2	40	56.5	2.5	0	22.0	10.5	2.5	6.0	III	++	+	+	0	
W. B.	29	F	4	6.5	70	2	28	71.0	0.5	0.5	9.0	8.5	6.0	4.5	III	++	+	+	0	
M. P.	37	F	2, 4	6.4	76	0	24	69.5	0.5	0.5	14.5	7.5	4.5	3.0	III	+++	++	+	0	
F. H.	39	M	6	9.0	54	1	45	53.0	1.0	0.5	14.0	12.5	4.5	14.5	III	+++	++	±	0	
M. W.	27	F	4	7.3	53	12	35	55.5	3.5	0	27.0	8.0	3.5	2.5	III	+++	++	0		
D. S.	23	M	1	7.1	60	10	30	60.5	10.5	1.0	7.5	11.0	1.0	8.5	III	++	++	++		0
S. M.	23	F	2, 3, 6	4.5	56	3	41	56.5	3.5	1.5	21.5	7.0	3.0	7.0	III	+++	+++	++	±	0
J. S.	29	F	2, 3	7.0	55	4	41	43.5	3.5	0	27.0	13.0	4.5	8.5	III	++	+	0		
S. L.	24	F	2, 3, 4, 5	7.7	51	11	38	56.0	8.0	1.5	11.0	13.0	1.5	9.0	II	+++	++	+	0	
J. B.	20	F	2, 4, 5	6.7	64	2	34	58.0	1.5	0	20.0	9.5	2.5	8.5	II	++	++	0		
F. M.	20	M	1	8.5	46	20	34	53.0	18.5	0.5	20.5	2.0	4.0	1.5	II	+++	++	±		
H. K.	27	F	2, 4, 5, 6	6.9	70	6	24	77.0	4.5	1.0	13.0	2.0	0.5	2.0	II	++++	+	0		
W. H.	21	M	2, 4, 5	4.6	63	5	32	55.5	5.5	1.5	20.5	10.5	3.5	3.0	II	+++	++	±		
M. D.	25	F	4	5.9	62	11	27	68.0	4.5	0.5	18.0	4.5	1.5	3.0	II	++	+	±		
I. K.	23	F	4	4.7	61	1	38	65.0	1.5	0.5	16.0	12.5	0	4.5	I	+++	+	+	0	
G. R.	34	F	6	6.0	69	1	30	59.0	1.0	1.0	21.0	15.0	1.0	2.0	I	++	++	+	0	
L. F.	28	F	1, 2, 3, 5, 6	4.4	50	5	45	42.0	11.0	1.0	17.5	14.0	5.0	9.5	III, II	+++	++	0		
H. B.	35	M	2, 3	5.3	57	8	35	41.0	5.0	0	21.0	21.0	3.0	9.0	III, II					
E. R.	36	F	2, 3	6.2	64	7	29	64.0	1.5	0.5	18.5	9.0	2.0	4.5	II, III	++	++	+	0	
D. M.	21	M	2, 5	10.4	77	5	18	61.0	7.0	0.5	13.5	10.0	5.5	2.5	II, III					
J. E.	22	M	2	7.2	62	1	37	68.0	1.0	0	14.0	11.0	3.0	3.0	I, III	+++	++	±	0	
V. B.	27	F	2, 5	6.9	65	1	34	70.5	4.5	0.5	13.5	9.0	1.0	1.0	I, III	+++	++	+	+	0

* 1, Atopic eczema; 2, allergic rhinitis; 3, bronchial asthma; 4, allergic headache; 5, gastro-intestinal allergy; 6, urticaria.

observed from the accompanying table, females of early adult type were in the majority. Many were nurses or persons of the hospital personnel who had been under careful medical supervision for an extended period. In 8 of the 25 cases, there was definite evidence of cervical gland enlargement, present at the time of the allergic study or observed upon some past occasion not readily explained.

Total and counting chamber differential leukocyte determinations were performed by the use of propylene glycol-aqueous stains, previously described.[9,10,11] A differential count of 200 cells from the standard Wright-stained cover slip and heterophil antibody determinations by the method of Paul and Bunnell[8] were done.

The atypical mononuclear cells observed in the films of these cases are similar morphologically to the 3 types of lymphoid cells in infectious mononucleosis as described by Downey.[4] Cells corresponding to his Type III are encountered most frequently. This cell has a very large nucleus, approximating the size of the nucleus seen in the blast forms of acute lymphatic leukemia, but differing from the latter in that the chromatin strands are more pronounced. Instead of the pale, evenly marked nucleus of the stained immature forms, the nucleus of this cell is more mottled due to slightly more clumping of the chromatin material. There are many sharply defined pale spots in the nuclei, unlike nucleoli, but suggesting holes through the nucleus. This feature has been described by Osgood[7] as "nuclear fenestrations." Nucleoli also appear occasionally.

Although the nucleus is invariably large, the amount of cytoplasm varies. The presence of many vacuoles in the cytoplasm of the larger cells gives them a characteristic foamy appearance. When less in amount, the cytoplasm is apt to be concentrated in a basophilic rim which is separated from the nucleus by a relatively clear zone. Although azurophil rods have not been observed, there often is an abundance of large, deeply stained azurophil granules and occasionally fine, azure granulation.

The Type II cells are slightly less common, but they occur in all the variations described by Downey. In some instances the nuclei are marked with several dense and sharply defined rounded masses of chromatin. The most common form (Downey's cell No. 7) contains a large irregular nucleus, appearing less immature than the nucleus of the Type III cells. The cell outline is angular and edges of the cytoplasm are irregularly basophilic. At times, only the points appear basophilic.

Downey's Type I cells were seen least frequently. These cells are relatively smaller than those of Types II and III. The nucleus is similar in size to that of the mature lymphocyte and may show marked lobulation; the chromatin exists in the form of a coarse network of heavy strands and masses. The cytoplasm is very basophilic and contains many vacuoles. Azure granulation is common and there is an abundant hyaloplasm.

The total number of mononuclear cells does not exceed the polymorphonuclears in any instance, as determined by either method of differential counting. The atypical lymphocytes range from 2 to 27%

of the total differential count. In several cases, the differential count was repeated at various times; atypical mononuclear cells were always observed, although the total number varied. In a small group of cases, serial counts were determined prior to and following the ingestion of foods known to produce allergic symptoms. Variations which occurred were inconstant and were not regarded as significant in view of the recognized errors in the distribution of large cells which occur in the preparation of the blood film.

Toxic granulation of the neutrophils accompanies the presence of atypical mononuclear cells in the majority of the films. This, incidentally, is a common finding in infectious mononucleosis.

Identical hematologic technique in a control series of 20 normal non-allergic individuals of similar age and sex distribution failed to reveal a significant number of atypical lymphocytes.[9]

Heterophil antibody determinations were normal in all instances in which the test was performed.

Discussion. The question is immediately raised whether the patients in this series might not be convalescing from infectious mononucleosis. Only one case (V.B.) was known to have had a past diagnosis of infectious mononucleosis. Two years earlier, her white blood count was recorded as 6000 cells, and the differential showed 28% neutrophils, 58% lymphocytes, 13% monocytes, and 1% basophils. The heterophil antibody reaction was strongly positive in a dilution of 1/256 and slightly positive to 1/512. She had been subject to hay fever for many years, and at the time studied was experiencing gastrointestinal symptoms of nausea, abdominal cramps and diarrhea which were relieved with milk avoidance and were precipitated at will by the ingestion of milk.

Seven of the remaining cases had been suspected of having had infectious mononucleosis in the past, but their heterophil antibody determinations had been consistently negative.

It is well known that abnormal lymphoid cells remain in the blood for appreciable periods after the active phase of infectious mononucleosis has subsided, and that the presence of abnormal lymphocytes in the routine blood examination may be evidence of infectious mononucleosis months or even years previously.[1,2] There is one case on record in which atypical cells characteristic of infectious mononucleosis occurred 10½ years after the original illness.[6]

We cannot state that the remaining 23 cases of this series had never had infectious mononucleosis; but this would appear unlikely, in view of the frequency with which we have observed these findings in cases of clinical allergy.

It is also well known that the presence of atypical lymphocytes in the peripheral blood is not diagnostic of infectious mononucleosis; such cells may occur in association with other disease processes. Warren[17] has recently reported finding cells characteristic of this disease, comprising between 1 and 10% of the differential count, in cases with upper respiratory infections, acute pharyngitis, or sinusitis. He also reported a group of cases having the clinical findings

of infectious mononucleosis with abnormal lymphocytes ranging up to 25% who lacked a significant heterophil response. The tendency of abnormal lymphocytes to enter the blood stream in cases with lymphoid hyperplasia other than infectious mononucleosis was pointed out by Baldridge, Rohner, and Hansmann[1]. The presence of atypical lymphocytes not associated with infectious mononucleosis has also been observed by others[5,15]

Summary. 1. The laboratory finding of atypical lymphocytes in the peripheral blood of patients with clinical allergy not infrequently suggests the diagnosis of infectious mononucleosis. The number of such cells is compatible with the blood findings in the recovery phase of this disease.

2. The symptoms of weakness, fatigue, and lassitude frequently characterize the allergic reaction, and commonly occur as sequelæ to acute infectious mononucleosis.

3. The fact that both conditions frequently occur in young adults otherwise in good health adds to the difficulties of differential diagnosis.

REFERENCES

1. Baldridge, C. W., Rohner, F. J., and Hansmann, G. H.: Arch. Int. Med., **38**, 413, 1926.
2. Bernstein, A.: Medicine, **19**, 85, 1940.
3. Coca, A. F.: Familial Nonreagenic Food Allergy, Charles C Thomas, 1943.
4. Downey, H., and McKinley, C. A.: Arch. Int. Med., **32**, 82, 1923.
5. Downey, H., and Stasney, J.: Folia hæmat., **54**, 417, 1936.
6. Farley, D. L.: Med. Clin. North America, **21**, 1139, 1937.
7. Osgood, E. E.: Proc. Soc. Exp. Biol. and Med., **33**, 218, 1935.
8. Paul, J. R., and Bunnell, W. W.: Am. J. Med. Sci., **183**, 90, 1932.
9. Randolph, T. G.: Proc. Soc. Exp. Biol. and Med., **52**, 20, 1943.
10. Randolph, T. G.: J. Allergy, 1944. In press.
11. Randolph, T. G.: In press.
12. Rinkel, H. J., and Balyeat, R. M.: J. Allergy, **3**, 567, 1932.
13. Rowe, A. H.: J. Allergy, **1**, 172, 1929.
14. Rowe, A. H.: Food Allergy, Its Manifestations, Diagnosis and Treatment; With a General Discussion of Bronchial Asthma, Lea & Febiger, 1931.
15. Stuart, S. A., Welch, H., Cunningham, J., and Burgess, A. M.: Arch. Int. Med., **58**, 512, 1936.
16. Vaughan, W. T.: J. Allergy, **5**, 501, 1934.
17. Warren, E. W.: Am. J. Med. Sci., **201**, 483, 1941.

RELATIONSHIP OF LYMPHOGRANULOMA VENEREUM INFECTION TO THE INCIDENCE OF HYPERGLOBULINEMIA

By Paul B. Beeson, M.D.
ASSISTANT PROFESSOR OF MEDICINE
AND
Edward S. Miller, M.D.
INSTRUCTOR IN MEDICINE
ATLANTA, GA.

(From the Medical Service of Grady Hospital and the Department of Medicine, Emory University School of Medicine)

An increase in the globulin fraction of blood serum is known to occur in certain diseases, among which are cirrhosis of the liver, lymphogranuloma venereum, sarcoid, multiple myeloma, kala azar, and some

acute infections. There is little information available regarding the general incidence of hyperglobulinemia, although this undoubtedly varies in different parts of the world. In Denmark it is apparently rare, as Bing[1] found only 7 instances of increased globulin among 3697 sera which had been submitted to a laboratory in that country for serologic tests for syphilis; this is an incidence of less than 0.2%. In localities where kala azar or lymphogranuloma venereum are prevalent hyperglobulinemia is undoubtedly more common.

The present study is concerned with the incidence of hyperglobulinemia in residents of Georgia. Our interest in this problem arose from observations made in a serologic study of the frequency of lymphogranuloma venereum infection in clinic patients. The findings in that study, which will be presented in detail elsewhere, are in accord with the general concept that lymphogranuloma venereum is far more common among negroes than among white people, and also that immunologic evidence of infection can often be obtained in the absence of a history or clinical sign of the infection. One finding which supported the specificity of the serologic test is the fact that many of the positive sera were also found to have an increased globulin content.

Because we had found hyperglobulinemia to be relatively common among the patients of one hospital it seemed of interest to determine the incidence of the condition in a less selected sample of people in the same locality. Accordingly we have carried out formol-gel tests on 2375 sera which had been submitted to the Central Laboratory of the Georgia Department of Public Health, for serologic tests for syphilis. The results are the subject of this paper.

Material. The specimens used had been sent by mail to Atlanta from various parts of Georgia. Some of them were from patients of private physicians or of clinics, while others were submitted as part of routine institutional surveys or examinations for military service. This group of sera cannot be called a random sample from the population in this area, but is nearer to a random sample than could be obtained in any other way. Our material is perhaps comparable to that of Bing[1] in Denmark.

Methods. Any serum which appeared cloudy, or which showed evidence of hemolysis, was rejected. Hyperglobulinemia was detected by means of the formol-gel test, in which a positive reaction indicates that the level of globulin is above 3.5 gm. per 100 cc. of serum.[2] Each test was set up by adding 2 drops of 37% formaldehyde to 1 cc. of serum in a 13 x 130 mm. test tube. The tube was stoppered, its contents mixed by inverting, and then allowed to stand at room temperature for 24 hours. Interpretation of the reaction was based only on gel formation; no account being taken of the development of oily consistency or cloudiness. The result was read as positive if the serum had gelled to such extent that more than half remained in the bottom of the tube upon inversion.

The complement-fixation test for lymphogranuloma venereum was done according to the technique of McKee *et al.*,[4] using as antigen the commercial egg yolk preparation, Lygranum C.F. (Squibb).

Results. The incidence of hyperglobulinemia, in relation to the race, sex and age of the persons from whom the blood specimens had been obtained, is shown in Tables 1 and 2. The most prominent finding is the marked racial difference: hyperglobulinemia was more than 10 times as frequent in the sera of negroes as in white persons.

TABLE 1.—INCIDENCE OF POSITIVE FORMOL-GEL REACTIONS, IN RELATION TO SEX AND AGE GROUP, IN THE SERA OF 1307 WHITE PERSONS

Age group	Males			Females		
	No. of sera	Formol-gel positive	%	No. of sera	Formol-gel positive	%
0–14	22	0	0	15	0	0
15–24	183	0	0	393	2	0.5
25–34	98	0	0	253	1	0.4
35–44	84	1	1.2	122	0	0
45 and over	62	1	1.6	75	2	2.7
Total	449	2	0.4	858	5	0.6

TABLE 2.—INCIDENCE OF POSITIVE FORMOL-GEL REACTIONS, IN RELATION TO SEX AND AGE GROUP, IN THE SERA OF 1068 NEGROES

Age group	Males			Females		
	No. of sera	Formol-gel positive	%	No. of sera	Formol-gel positive	%
0–14	22	3	13.6	37	0	0
15–24	174	10	5.7	265	20	7.5
25–34	188	9	4.3	152	18	11.8
35–44	73	2	2.7	78	4	5.1
45 and over	46	4	8.7	33	5	15.1
Total	503	28	5.6	565	47	8.3

We believe that a difference in the prevalence of infection with lymphogranuloma venereum must be directly related to the racial difference in incidence of hyperglobulinemia. All studies, including our own, indicate that this disease is much more frequent in negroes. Other causes of hyperglobulinemia, such as liver disease, sarcoid and multiple myeloma do not appear to manifest any such racial affinity; furthermore none of them is sufficiently common to affect 5 to 8% of the general population at one time.

In regard to sex incidence, hyperglobulinemia was found in a slightly higher proportion of females than of males. The total number of positive sera from white people was so small that this difference cannot be regarded as significant; but in the case of the negroes, where increased globulin was relatively common, the higher incidence found in females may be significant—perhaps it is a reflection of the different forms which the disease assumes in females and males.

It seems unadvisable to draw any conclusion from the age distribution of the cases of hyperglobulinemia in this series, because the numbers of persons in some of the groups are small. A case of acute rheumatic fever in a child or of liver disease in an older person could easily obscure the picture of hyperglobulinemia due to lymphogranuloma venereum, despite the fact that that disease is probably the principal cause of the condition in the present series.

In Table 3 the incidence of hyperglobulinemia is compared with the result of the serologic tests for syphilis. This shows that increased globulin was more frequent in the sera of persons with syphilis. (The data on white persons are not included because there were only 93 Kahn-positive sera from white persons; 1 of these gave a positive formol-gel test). One might infer from the data in Table 3 that syphilis is a frequent cause of hyperglobulinemia; however, there is

considerable evidence available indicating that such is not the case.[3] A more probable explanation of the relationship is simply that persons who have acquired one venereal disease are apt to have acquired another. This view is supported by the results which we obtained when some of the same sera were tested for complement fixation with lymphogranuloma venereum virus. One hundred and thirty Kahn-positive sera, all from negroes, were tested. In 5 of them the result could not be determined because of reaction with the antigen control, a difficulty which is encountered occasionally in syphilitic sera.[5] Of the remaining 125 sera, 74 gave a positive test for lymphogranuloma venereum, while 51 were negative. In these 2 groups there were 13 cases of hyperglobulinemia; 12 of them were from persons with lymphogranuloma venereum, while only 1 was from a person with syphilis alone. This appears to be a significant difference, and points to lymphogranuloma venereum rather than to syphilis as the principal cause of hyperglobulinemia.

TABLE 3.—INCIDENCE OF POSITIVE FORMOL-GEL REACTIONS, IN RELATION TO RESULT OF KAHN TEST FOR SYPHILIS; SERA FROM 1068 NEGROES

Age group	Kahn-positive			Kahn-negative		
	No. of sera	Formol-gel positive	%	No. of sera	Formol-gel positive	%
0–14	5	1	20.0	54	2	3.7
15–24	169	16	9.5	270	14	5.2
25–34	206	23	11.2	134	4	3.0
35–44	84	5	6.0	67	1	1.5
45 and over	21	4	19.0	58	5	8.6
Total	485	49	10.1	583	26	4.4

Summary. Because of the prevalence of lymphogranuloma venereum in the negro population in Georgia, a study was made of the incidence of hyperglobulinemia in 2375 sera, from both the white and the negro population. The formol-gel test was used to detect the presence of increased globulin. Hyperglobulinemia was found in 0.4% of white males and in 0.6% of white females. In negroes the respective rates were 5.6% and 8.3%. The difference in prevalence of lymphogranuloma venereum infection is presumed to be the explanation of this racial difference. A higher proportion of cases of hyperglobulinemia found among negroes with syphilis appeared to be related to the associated presence of lymphogranuloma venereum in those persons.

We are indebted to Miss Med Scott Brown for technical assistance in this work. We wish to thank Dr. T. F. Sellers, Director, and Messrs. E. L. Webb, Chief Serologist and C. S. Adams, Assistant Serologist of the Georgia Department of Public Health Laboratories, for their coöperation, which made this study possible.

REFERENCES

1. BING, J.: Acta med. Scandinav., **91**, 336, 1937.
2. CARDON, L., and ATLAS, D. H.: Arch. Int. Med., **71**, 377, 1943.
3. JONES, C. A., and ROME, H. P.: Am. J. Clin. Path., **9**, 421, 1939.
4. MCKEE, C. M., RAKE, G., and SHAFFER, M. F.: Proc. Soc. Exp. Biol. and Med., **44**, 410, 1940.
5. SHAFFER, M. F., RAKE, G., GRACE, A. W., MCKEE, C. M., JONES, H. P.: Am. J. Syph., Gonor. and Ven. Dis., **25**, 699, 1941.

CHLOROPHYLL: AN EXPERIMENTAL STUDY OF ITS WATER-SOLUBLE DERIVATIVES*

I. Remarks Upon the History, Chemistry, Toxicity and Antibacterial Properties of Water-Soluble Chlorophyll Derivatives as Therapeutic Agents

By Lawrence W. Smith, M.D.
Professor of Pathology
Philadelphia, Pa.

(From the Temple University School of Medicine)

In recent years interest in the possible therapeutic value of various chlorophyll derivatives has been revived, after a hiatus of nearly a quarter of a century. Up to the present time, however, such evidence as has appeared in the literature has been so relatively scanty and inadequately controlled, that it seemed worth while to attempt to explore certain aspects of the problem by well established experimental methods in an attempt to evaluate its potentialities clinically. To this end, a number of experiments were designed and carried out to determine certain more or less specific facts regarding the nature and manner of action of therapeutic preparations made with stable, purified, water soluble chlorophyll derivatives.†

In the first place, it seemed important to establish whether or not the chlorophyll‡ derivatives were toxic. Second, studies regarding the bactericidal or bacteriostatic effects of these derivatives seemed definitely indicated, in view of the favorable reports which had appeared in respect to its benefits in a wide variety of infectious conditions. Third, the effect of chlorophyll as a growth stimulating agent, in comparison with other substances in current use or under investigation at the present time in the repair of wounds of both traumatic and thermic origin, seemed of particular importance to ascertain, in view of its very great practical interest in the war program. In addition to these 3 main aspects of the problem, it was hoped that incidental accumulated data from these studies might yield further information as to the mechanism of the action and fate of chlorophyll in the body and any possible effect it might have upon the hematopoietic system through its close structural composition to that of hemoglobin.

Chemistry of Chlorophyll.§ Chlorophyll, the green coloring matter of plants, has stirred the imagination of biologists through the centuries. It is perhaps but natural that the greatest interest has been exhibited

* Aided by a grant from the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association.

† The experimental products were generously supplied us by the Rystan Company of New York City, sole licensee of the Lakeland Foundation, Chicago, in accordance with the regulations of the Food and Drug Administration regarding new experimental therapeutic agents.

‡ Wherever the term "chlorophyll" is used in these studies the water-soluble derivatives are meant, the term "chlorophyll" being used for the sake of brevity.

§ I am indebted to Prof. Paul Rothemund of Antioch College and to Isidor Chamelin, M.S., of the Goldwater Memorial Hospital, Welfare Island, New York City, for their kindness in reviewing and revising the section relating to the chemistry of chlorophyll.

by those scientists concerned particularly with plant physiology, and above all, by the biochemists, who have sought to understand the complex mechanism of the conversion of carbon dioxide to starch by plants through photosynthesis and the action of chlorophyll. Even among the ancients, the greenest herbs were chosen for their crude empiric remedies. But it was not until Willstätter and Stoll's[23] (1913) monumental studies upon chlorophyll that its empirical formula was established. Since that time, the further studies of Stoll,[19] Conant, Hans Fischer[6,7] and others[1,5,9,13–15,18,20–23] have established the molecular formula (see Fig. 1). The unfolding of our knowledge regarding the chemistry of chlorophyll will be found in the publications listed in the appended bibliography.

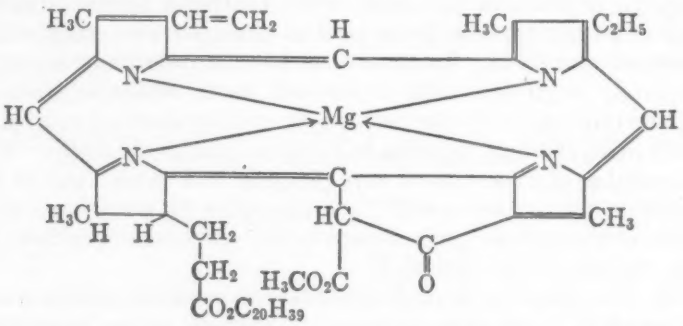


FIG. 1.—The structural formula for chlorophyll *a*, as determined by Hans Fischer.[7]

Chlorophyll, from present knowledge, consists of two components: chlorophyll *a* ($C_{55}H_{72}O_5N_4Mg$) and chlorophyll *b* ($C_{55}H_{70}O_6N_4Mg$). These components occur in nature in an almost invariable proportion of 2.9:1. They are relatively inert blue-black substances with a marked metallic luster. They have no definite melting points, varying from 117° to 120° C. for the *a* form and 120° to 130° C. for the *b* form. Both forms are optically active: the specific rotation of the *a* form is at −262° and of the *b* at −267°. The two fractions are neutral in reaction, with neither acidic nor basic properties.

Examination of the structural formula of chlorophyll *a* (Fig. 1) as determined by H. Fischer[7] (1939) shows the substance to be a diester:

$$C_{32}H_{30}N_4OMg \begin{cases} COOCH_3 & \text{(Methyl)} \\ COOC_{20}H_{39} & \text{(Phytyl)} \end{cases}$$

The phytyl group is placed on the proprionic acid residue of pyrrole nucleus IV while the carbmethoxy group is attached to the isocyclic ring (C_{10}).

The formula of chlorophyll *b* as it is known at present, has an aldehydic or formol group on C_3 in place of the $-CH_3$ of chlorophyll *a*. This substitution yields 2 hydrogen atoms less and 1 oxygen atom more than in the chlorophyll *a* structure.

Treatment of either chlorophyll with mild acids, such as oxalic acid, removes the nuclear magnesium. More vigorous acid action removes the phytyl radical in addition.

The degradation products run parallel in the *a* and *b* components forming pheophytins *a* and *b;* pheophorbides *a* and *b;* chlorins from *a* and rhodins from *b*. The porphyrins and further degradation compounds are the same whether obtained from chlorophylls *a* or *b*.

The chlorophylls are easily soluble in absolute ethyl alcohol, somewhat less soluble in 95% ethyl alcohol as well as in methyl alcohol. They are not soluble in petroleum ether.

Chlorophyll may be obtained from either fresh or dried leaves by extraction with acetone. It occurs in greatest concentration probably in nettles, alfalfa and spinach. A kilo of fresh leaves yields about 1.5 gm. of chlorophyll on the average, while about 7.5 gm. can be obtained from a kilo of dried leaves. In its natural state it occurs in colloidal form. As isolated from plants it is amorphous in character (phytylchlorophyllide), but it can be secured in crystalline form (methyl or ethyl chlorophyllide) through the substitution of the phytyl radical by the respective alcohol either through chlorophyllase enzymic action or by alcoholic extraction.

The similarity of hemoglobin and chlorophyll is seen in the comparison of the hematin and chlorophyll molecules as described by Gortner.[9] In hemoglobin, iron is substituted for the magnesium of chlorophyll, globin is substituted for the phytyl radical, and at Carbon 4 an allyl instead of an ethyl residue is obtained.

The water-soluble chlorophyll used in these experimental studies, as supplied by the Rystan Company, is a medicinally purified product, from which the resins and other impurities have been removed as far as possible by adsorption. In the main we used a saponified metal complex derivative of chlorophyll, such as sodium copper chlorophyllin. It has been provided in two forms: (1) as saline solutions in strengths ranging from 0.2 to 5%, and (2) as ointments in lanolin, cholesterol and hydrophilic bases. Both types of product as used experimentally and clinically, have had a preservative, propyl-para-hydroxy-benzoate, added in small amounts; but for bacteriologic and tissue culture experiments, sterile material has been given us without such added preservative. The pH of the solution has varied also in the products for clinical use—that for nose and throat work being buffered to approximately pH 6.7, while the ordinary, unbuffered solution has had a pH which ranged from 7.3 to 8.5 The standard ointment has contained 1% of the water-soluble chlorophyll although earlier preparations varied in their chlorophyll content from 0.25% to 3% in an attempt to find the optimal concentration.

Most previously published clinical studies have been concerned with the oil-soluble product.[2,3,12] Experience over a period of years has convincingly demonstrated that the water-soluble derivatives are much preferable in clinical use, as they are equally, if not more effective,[10] than the oil-soluble form and at the same time are bland and non-irritating. The oil-soluble fraction also presents certain obvious objections to its use: it does not lend itself readily to use on mucous membranes; it is difficult to obtain in pure form, and it tends to be slightly irritating, presumably due to impurities. For these reasons, we have elected to use aqueous-soluble products in these studies.

Toxicity Studies. In a series of 20 rabbits—chlorophyll (provided as a 0.2% saline solution with a pH of 7.3) was administered: (*a*) by mouth, (*b*) intravenously, (*c*) intraperitoneally and (*d*) subcutaneously, separately and in combination. It has likewise been given in a smaller series of 5 rabbits (*a*) by mouth and (*b*) intravenously in concentrated form (2%).

Method. The dosage has varied from 5 cc. subcutaneously to as much as 150 cc. intravenously at one time. The majority of the animals have been given the drug intravenously and in repeated dosage. The usual interval was 5 days and the average single dose was 50 cc. In 2 animals this amount was administered daily for 5 days. One animal received a total of 550 cc. in 8 doses at 5-day intervals, the first 6 being 50 cc., the 7th dose 100 cc., and the 8th dose 150 cc. In several of the animals, as a purely side observation, the effect upon hematopoiesis was noted by removing a corresponding volume of blood before the drug was given, and following the blood count at intervals.

None of the animals given chlorophyll in any of the experiments, regardless of the dosage, showed any systemic reaction indicative of toxic effect. There was no elevation of temperature and no significant gastro-intestinal symptomatology other than a slight diarrhea in an occasional instance. Their appetite was not affected, nor was their physical activity. The red cell count returned to normal within 4 or 5 days in these animals which were bled as much as 50 cc. repeatedly. This would suggest that the drug might perhaps have some actual stimulating effect upon hematopoiesis.

Pathologic examination of several of the animals show considerable retention of the pigment in the reticulo-endothelial system, notably the spleen and bone marrow. Whether this might eventuate in reticulo-endothelial block under such extreme experimental dosage cannot be answered at this point; but, as reported by Henderson and Long[11] as well as in our experience, there is no evidence to suggest that this does occur. Our impression, at present, is rather that any effect which takes place is in the nature of cell stimulation.

The chlorophyll solution likewise has been given intravenously to a number of dogs, cats, guinea pigs, rats and mice with essentially similar negative results so far as any toxic effect is concerned. No attempt has been made in these animal experiments to evaluate the drug therapeutically in any way. They were concerned solely with an investigation of its toxicity.

Clinically, 240 cc. of the 2% solution has been given daily for 3 days by mouth to a normal healthy adult male volunteer. No subjective or objective symptoms or signs occurred other than a slight increase in bowel evacuation, the stool being somewhat softer than normal, and somewhat discolored by the drug. In addition, as much as 500 cc. of 0.5% chlorophyll solution has been administered intravenously daily for 8 days in cases of subacute bacterial endocarditis with no toxic symptoms, and with some temporary bacteriostatic effect.

As regards toxicity, we can conclude without qualification that such medicinal water-soluble chlorophyll derivatives as are contained in the preparations we have employed in these studies are without any toxic effect upon the usual laboratory animals or on man.

Bacteriologic Studies.* In view of the striking results, as reported by several clinics[2,3,8] and numerous doctors who have investigated these same water-soluble chlorophyll preparations during the past 3 or more years, in reducing or eliminating the infections associated with many ulcerative lesions, both clinical and as induced in experimental wounds in animals,[4] it was felt that a survey of the antibacterial properties of chlorophyll *in vitro* was indicated. *A priori*, one might expect that chlorophyll, being derived from plants, and possessing certain cellular growth stimulating properties as demonstrated in tissue culture[17] and wound healing experiments,[16] would tend similarly to accelerate rather than inhibit bacterial growth. Yet the evidence seems to indicate that chlorophyll exerts a definite bacteriostatic effect upon many of the common tissue invaders; and even an actual bactericidal effect upon some of the more delicate organisms, notably Lancefield Type A hemolytic streptococci and some of the anaerobic bacteria. In this connection Henderson and Long[11] have shown recently that "phytorhodin g" has a definite inhibitory effect upon the growth of tubercle bacilli in culture, but that it does not materially alter the course of the experimentally induced disease in guinea pigs, although it tends to localize the extent of the process.

Preliminary studies revealed that chlorophyll alone in dilutions of from 1:100 to 1:500 would not support the growth or even the viability of staphylococci, streptococci or coliform bacteria over a period of 24 to 48 hours. Dilutions of chlorophyll up to 1:2000 in a brain-heart broth medium showed a definite bacteriostatic effect upon the growth of these organisms although growth was not completely inhibited in this medium beyond a 1:500 dilution.

Method. On the basis of the results of these preliminary experiments somewhat more extensive tests were made, using beef infusion broth as the medium, and increasing the inoculum to average 90,000 organisms.

1. *Staph. aureus* was inhibited by 1:80 dilution, but not by 1:160. It was not killed by 24 hour exposure to 1:20 dilution.
2. *Strep. hemolyticus* was inhibited by 1:640 dilution, but not by 1:1280. It was killed also by the 1:640 dilution.
3. *Esch. coli* was not inhibited by the 1:20 dilution.
4. No evidence of morphologic variation noted except a tendency for the streptococci to become gram negative after 7 days.

It was felt wise to extend these bacteriologic studies a little further to include certain of the anaerobic organisms and *Ps. pyocyaneus*. The prompt deodorization and cleaning up of infected, ulcerated lesions, such as carcinoma and varicose ulcers, clinically, often within a matter of 48 to 96 hours, prompted this line of attack in an effort to attempt to explain the action of chlorophyll in such cases.

In these experiments 8 organisms were employed, varying the amount of the inoculum, and the type of media. The organisms used were:

1. *Staph. aureus*, a highly hemolytic, coagulase positive strain fermenting lactose and mannite, No. 209.

* The bacteriologic studies were carried out through the coöperation and supervision of E. H. Spaulding, Ph.D., Associate Professor of Bacteriology.

2. *Strep. hemolyticus*, Group A—recent isolation.
3. *Strep. hemolyticus*, Group A—strain C-203.
4. *Strep. mastitidis* (agalactiae), Group B—recently isolated from an infected herd of cattle, through the courtesy of Dr. Oscar Erf of Ohio State University.
5. *Ps. pyocyaneus*, a recent isolation.
6. *Esch. coli*, freshly isolated hemolytic strain.
7. *Cl. perfringens*, a Sharp & Dohme strain No. 1633.
8. *Cl. histolyticum*, A. T. C. C. No. 6282.

Initially, veal infusion, and 1% amigen broth were employed. The inoculum averaged about 9000 colonies except in the case of the two anaerobes in which it was only about 1000 colonies. Inhibition of growth of *Esch. coli* and *Ps. pyocyaneus* was noted in 1:50 dilutions; of *Strep. mastitidis* in 1:200 dilution, of the streptococci, and the two anaerobes in 1:1600 dilution and no inhibition of the hemolytic staphylococcus was obtained. The experiments were repeated increasing the inoculum with approximately the same results.

This apparent bactericidal effect of chlorophyll upon anaerobic bacteria as suggested by these last outlined experiments could be explained as dependent upon an oxidizing mechanism. To test this hypothesis, these tests were repeated using this time, however, (Brewer's) thioglycollate medium which does not require the use of an anaerobic jar, and which contained as a constituent, an oxidation-reduction indicator, methylene blue. Control experiments using the medium alone with the addition of chlorophyll in dilutions of from 1:10,000 to 1:40,000 were made. The results indicated that chlorophyll was unable to oxidize the thioglycollate medium appreciably, and its inhibiting effect upon the growth of *Cl. perfringens* and *Cl. histolyticum* was sharply reduced, being ineffective in dilutions of 1:500.

These results were in such striking contrast to those obtained earlier with veal infusion broth that it was thought advisable to repeat the earlier experiments adding a reducing agent, cysteine hydrochloride, to the veal broth medium. This had a final concentration of 0.02%. Again it was demonstrated that chlorophyll was unable to prevent the reduction of the methylene blue in the presence of such small amounts of cysteine hydrochloride, and that the inhibition of anaerobic bacterial growth was strikingly reduced, although in this case stasis was obtained for 48 to 72 hours in dilutions of 1:500 and 1:1000. These studies suggest that some interference with the oxidation-reduction mechanism of bacterial respiration is produced by the action of chlorophyll, which might well account for its bacteriostatic and even bactericidal effect clinically in a large proportion of cases.

Discussion. Studies on the effect of water-soluble chlorophyll preparations on cultures of various of the more common pathogenic bacteria tend to support the premise that chlorophyll acts to produce an unfavorable environment for bacterial growth rather than by any direct action upon the bacteria themselves. However, it is to be noted that the ordinary pyogenic bacteria will neither grow nor survive for 24 hours in simple isotonic saline solutions of chlorophyll up to dilutions of 1:500.

The experiments point towards an oxidation mechanism as perhaps most readily explaining the ability of chlorophyll to hold back anaerobic bacterial growth. The addition of reducing agents such as cysteine or thioglycollate to the medium in sufficient amounts overcomes this action and again permits growth to take place. Thus, there appear to be not only qualitative but also quantitative factors to consider in attempting to interpret the almost regular improvement of the infectious picture in clinical cases where chlorophyll is applied topically. Whether some mechanism which interferes with bacterial respiration exists similar to that occurring in relation to the sulfa compounds in infection requires further investigation.

Whether the prompt tissue repair response to chlorophyll therapy may not be the chief *modus operandi* in its control of infection seems entirely probable. At all events, it can be said as a result of these bacteriologic studies that chlorophyll is not strictly bactericidal, but that it does exert a definite bacteriostatic and even a bactericidal effect under suitable environmental conditions. When time and opportunity permit, these problems should be pursued to their ultimate solution, as the place of chlorophyll in the entire biologic pattern is so universally important that a thorough understanding of its mechanism is most essential.

Summary. 1. A brief résumé of our current concepts regarding the composition and chemical behavior of chlorophyll is presented.

2. Experimental evidence is introduced to demonstrate the total absence of toxic effects of the water-soluble derivatives of chlorophyll when administered, subcutaneously or intravenously, to animals or man.

3. Bacteriologic studies are reviewed which point towards an interference with the oxidation-reduction mechanism of bacterial respiration as explaining the rather striking bacteriostatic effects noted in the use of water-soluble chlorophyll derivatives clinically, and experimentally in animals, in the treatment of infected surface wounds.

REFERENCES

1. Adams, E. Q.: J. Am. Chem. Soc., **48**, 292, 1926.
2. Boehringer, F.: Schwerz. med. Wchnschr., **72**, 850, 1942; Abstr., J. Am. Med. Assn., **121**, 793, 1943.
3. Buergi, E.: Abstr., J. Am. Med. Assn., **121**, 1237, 1943.
4. Brush, B. E., and Lam, C. R.: Surgery, **12**, 355, 1942.
5. Fischer, F. G., and Löwenberg, K.: Ann. Chem., **464**, 69, 1928.
6. Fischer, H., and Orth, H.: Halfte Akademische Verlagsgesellschaft M. B. H., Leipzig, 1940.
7. Fischer, H., and Wenderoth, H.: Justus Liebigs Annalen der Chemie, **537**, 170, 1939.
7*a*. Gilman, H.: Organic Chemistry, 2nd ed., New York, John Wiley & Sons, **2**, 1308, 1943.
8. Goldberg, S. L.: Am. J. Surg., **42**, 117, 1943.
9. Gortner, R. A.: Outlines of Biochemistry, 2nd ed., New York, John Wiley & Sons, Chap. 30, pp. 732–739.
10. Gruskin, B.: Personal communication.
11. Henderson, H. J., and Long, E. S.: Proc. Soc. Exper. Biol. and Med., **43**, 435, 436, 1941.
12. Holmes, G. W., and Mueller, H. P.: Am. J. Roentgenol. and Rad. Ther., **59**, 210, 1943.
13. Inman, O. L.: History of Randleigh Farm, Lockport, N. Y., Wm. R. Kenan, Jr., Chap. XXXIII, pp. 285–288, 1937.

14. MAYER, F., and COOK, A. H.: Chemistry of Natural Coloring Matters, New York, Reinhold Publ. Co., 1943; Am. Chem. Soc. Monograph No. 89, pp. 295–327.
15. SCHERTZ, F. M.: Plant Physiol., **3**, 211, 323, 487, 1928.
16. SMITH, L. W., and LIVINGSTON, A. E.: Am. J. Surg., **62**, 355, 1943.
17. SMITH, L. W.: J. Lab. and Clin. Med. **29**, 241. 1944.
18. STEELE, C. C.: Gilman's Organic Chemistry, 2nd ed., New York, John Wiley & Sons, **2**, 1293, 1943.
19. STOLL, A.: Naturwissenschaften, **20**, 889, 1932.
20. STOLL, A., and WEIDEMANN, E.: Naturwissenschaften, **20**, 889, 1932.
21. WEST, C. J.: Biochem. Bull., **3**, 229, 1914.
22. WILLSTÄTTER, R.: J. Am. Chem. Soc., **37**, 323, 1915.
23. WILLSTÄTTER, R., and STOLL, A.: Untersuchungen über Chlorophyll (monograph), Berlin, Springer, 1913.

A TUMOR OCCURRING IN THE SUPERIOR PULMONARY SULCUS

By IRVING IMBER, M.D.
RESIDENT IN PATHOLOGY
READING, PA.

(From the Departments of Pathology, Radiology and Medicine, The Reading Hospital)

SINCE the publication of a paper, "Superior Pulmonary Sulcus Tumor," by Dr. Henry K. Pancoast in 1932,[16] considerable controversy has arisen as to the origin and classification of the tumors which he described. Several writers[1,3,5,9,13,15] have expressed the opinion that the entire syndrome described by Pancoast could be produced by any inflammatory process or tumor mass arising within the lung or in the pulmonary sulcus. Some authors[10,14,15,18] have suggested that most tumors of this nature are bronchogenic or pulmonary in origin. Other authors[2,7,8,16,17] have attempted to present evidence to show that the tumors which they described arose outside the lung and pleura in the superior pulmonary sulcus, thus supporting the original contention of Pancoast. Dr. Joseph McFarland[12] has suggested a possible origin in the precervical sinus for the latter group.

Hall,[9] in a thorough review of the literature, has suggested that in most of the reported cases the lesion is an apical bronchogenic carcinoma with secondary involvement of the brachial plexus and the cervical sympathetic chain. Sympathicoblastomas,[6,11] dural epithelioma of cord[11] squamous cell epithelioma[5] and metastatic carcinoma[4,9,18] have all been reported as producing an anamnesis and clinical course similar to the pulmonary sulcus syndrome.

The following case report and postmortem study is considered worthy of publication because it illustrates a superior pulmonary sulcus tumor in which the extrapulmonary origin of the tumor can be established, thus favoring the original contention of Pancoast that a primary tumor may arise in the pulmonary sulcus and that it may produce a definite clinical syndrome.

Case Report. B. R., white, male, age 47, American, electrician, was admitted to the hospital on Dec. 4, 1942, complaining of pain in his right scapular area and cough. He was in his usual good health until 2 months before admission, when he first noted a sharp piercing pain in his back medial to the right scapula. This pain soon became more constant, boring and aching in nature, and seemed to travel down the right arm. The arm then became numb and weak. Since the onset of this pain, he had a morning cough pro-

ductive of a moderate amount of yellowish white mucus and noted dyspnea on exertion. In the 2-month period prior to hospitalization he had lost 20 pounds in weight and complained of marked anorexia and weakness. Afternoon and night sweats were present, but never any hemoptysis. The systemic review, medical, social and family histories were entirely irrelevant.

Physical examination revealed a thin, pale, middle-aged, white man in apparent distress. His weight was 122 pounds and his sensorium was clear. A typical Claude Bernard-Horner's syndrome was present on the right. The right arm showed a moderate amount of muscular atrophy and a definite decrease in muscle power. Pain sensation was diminished in the right hand and forearm. The biceps, triceps, radial and ulnar reflexes were exaggerated on the right. Examination of the chest revealed dullness to percussion at the right apex and a diminution in breath sounds in that area. A definite tumor

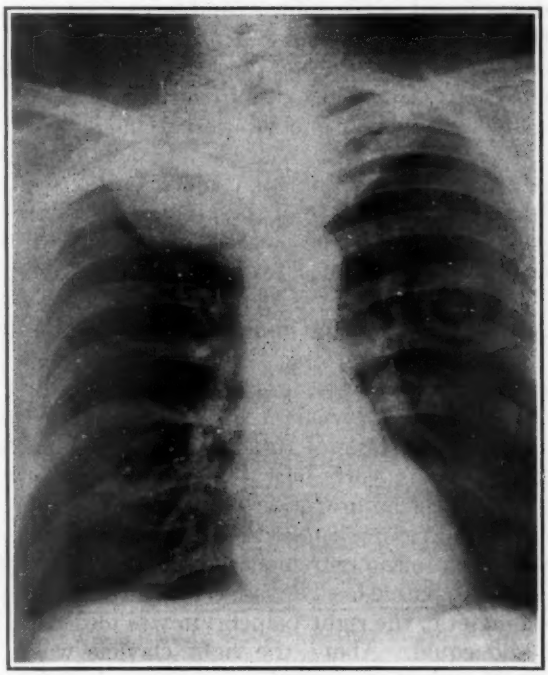


FIG. 1.—Chest demonstrating definite growth in the right apex.

mass was palpated in the supraclavicular area on the right. The heart size was within normal limits, and the rate, rhythm and sounds were normal. Blood pressure was 104 over 44 in both arms with only slight variation on several readings. Examination of the abdomen revealed nothing abnormal. Sputum examination was repeatedly negative for acid-fast bacillus and blood. The blood Wassermann reaction was negative. Urinalysis was negative. Erythrocytes, 3,320,000; hemoglobin, 63%; leukocytes, 15,200, with 79% neutrophils, 20% lymphocytes and 1% eosinophils.

The *Roentgen examination* (Fig. 1) showed a lesion involving the apex of the right upper thorax. The lesion was indicated by a sharply defined, rounded, soft tissue shadow approximately the size of a tennis ball. This extended as low as the second rib anteriorly and filled the apex of the thorax. It displaced the esophagus slightly to the left but did not produce any evidence of erosion of the ribs or vertebræ.

When the patient was presented to the hospital tumor conference, the differential diagnosis of primary and metastatic malignancy was discussed, but no definite conclusions were reached. The radiologist suggested that the lesion was a primary growth possibly originating in the smaller bronchi of the right upper lobe. Operation was suggested as the treatment of choice for the purpose of biopsy and, if possible, lobectomy. After transfer to the Hamburg Tuberculosis Sanitarium for lobectomy further radiographic examinations were made of the chest. These showed an increase in the size of the tumor mass, but no bone erosion could be ascertained. A bronchoscopic study revealed a normal tracheobronchial tree with moderate compression of the trachea by an external lesion. On January 4, 1943, occult blood was found in the sputum and feces. Radiographic examination of the intestinal tract showed no definite lesion. About this time a walnut-sized mass appeared over the first interspace at the left sternal edge. Biopsy from this mass by Dr. A. Judd was reported by Dr. E. D. Funk as probable metastatic carcinoma of squamous cell origin.

With the general picture of rapid deterioration, erosion of the sternum, and rapidity of growth of the pulmonary lesion, a lobectomy was considered foolhardy. The patient was returned to the Reading Hospital on Jan. 14, 1943, in a cachectic state and expired shortly thereafter. Just previous to his demise on Jan. 22, 1943, two soft tissue nodules were noted in the upper abdominal wall.

Necropsy Findings. *Macroscopic.* Superior pulmonary sulcus tumor with erosion of the manubrium, first and second ribs, first and second thoracic vertebra, and involvement of the brachial plexus and sympathetic ganglion; metastasis of tumor to skin, peritoneum and right and left adrenal medulla; early bronchopneumonia of right lower lobe; inanition; pathologic fracture of first rib on right side; pulmonary emphysema; chronic passive congestion of liver and spleen.

The body was that of an extremely emaciated white male, weighing approximately 100 pounds. The skin had a sallow, yellow color. The sclera was icteric, the right palpebrum was closed and the pupils were round and equal. Above the right clavicle was a protruding apical mass. The chest was emphysematous. Just lateral and left to the manubrium was a nodular growth measuring 4 x 5 x 1.5 cm. with a healed incision over its surface measuring 4 inches in length. The abdomen was scaphoid in type. Below the rib margin in the right and left mid-clavicular line were two hard nodular masses. Another mass over the right hip was also noted.

When the peritoneum was opened a large cauliflower mass measuring 5 x 5 x 3 cm. was found anteriorly in the abdominal wall just above and lateral to the umbilicus. No free fluid was found. The intestinal tract was collapsed and normal throughout. The right anterior abdominal wall contained a nodular mass beneath the peritoneum which measured 3 cm. in diameter. These growths were friable, necrotic and yellow in color.

The right pleural cavity contained a tumor mass lying in the extreme apical portion. It was fungating, friable, necrotic, yellowish white in

color, and measured 9 x 8 x 5 cm. *in situ*. The apical portion of the upper lobe was attached to the mass by adhesions which were readily broken. The mass extended anteriorly to the level of the second rib and posteriorly to the fourth interspace. It had eroded through the first and second ribs, causing a pathologic fracture of the first rib, and also into the first and second thoracic vertebræ. It extended superiorly into the brachial plexus to the level of the cricoid cartilage.

The right lung measured 23 x 22 x 5 cm. and weighed 610 gm. At the apex there was a scarred area measuring 8 x 8 cm. which was attached to the tumor mass. In this area the lung parenchyma was compressed and no evidence of tumor could be found on gross section. Several small, patchy, yellowish red areas were present at the base. The bronchioles were filled with a yellowish exudate.

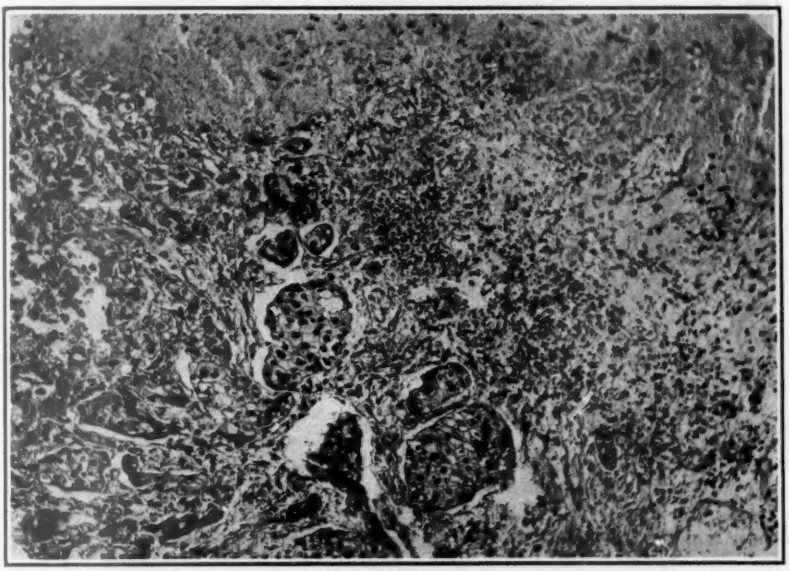


FIG. 2.—Sulcus tumor showing cellular degeneration and round cell infiltration. (× 150.)

The right adrenal gland measured 8 x 6 x 3 cm., and the medulla was replaced by a large, fungating, yellowish white mass of necrotic tumor tissue. Only a narrow strip of yellowish orange cortical substance remained. The left adrenal measured 6 x 5 x 3.5 cm. and showed the medulla replaced by a growth similar in gross appearance to that in the medulla of the right adrenal.

The left and right kidneys presented a flattened area in the superior pole where the suprarenal glands had rested. They were entirely free of the adrenals and showed no evidence of any tumor growths. The cortex and medulla were well differentiated and the capsule stripped with ease.

The testes, epididymis and prostate gland were all small and normal in appearance.

Microscopic. Study of the sulcus tumor mass revealed extensive cellular necrosis in which were found islands and masses of tumor cells (Fig. 2). The cellular portion of the tumor was composed of irregularly shaped large cells with a slightly granular or clear cytoplasm and a large round or oval vesiculated nucleus with a prominent nucleolus. Some nuclei, however, were pyknotic and hyperchromatic. No tendency toward any definite acinar formation of the tumor cells was noted (Fig. 3). Throughout these masses of tumor cells, lymphocytes were diffusely scattered. In the center of a number of islands of these immature squamous epithelial cells was an area of cellular necrosis

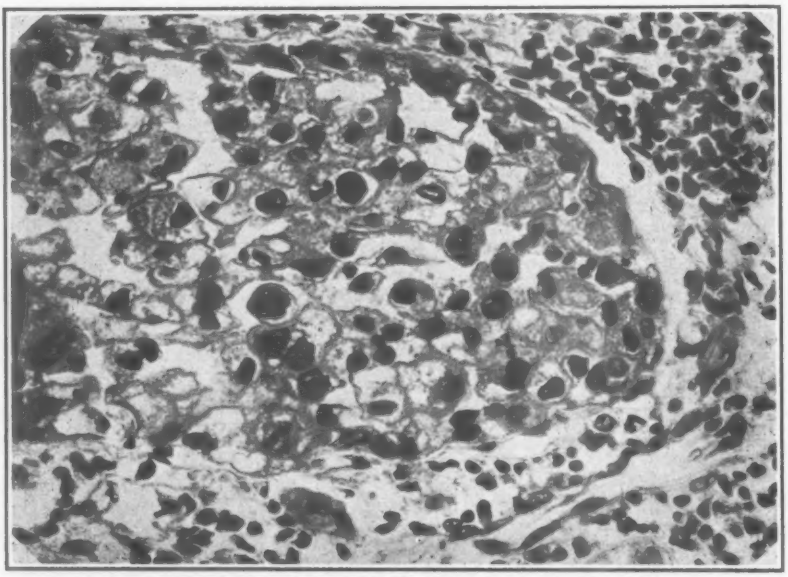


FIG. 3.—Neoplastic area showing mitosis and anaplasia. (× 640.)

which was surrounded by round cells. Mitotic figures were frequent. The underlying lung, which was attached by fibrous connective tissue to the tumor, revealed an infiltration of round cells, tumor cells, and a partial atelectasis of the alveoli. Several bronchioles were present. These showed no evidence of any malignant degeneration. The lung tissue of the right lower lobe revealed a patchy bronchopneumonia. Here the alveoli were filled with polymorphonuclear leukocytes and monocytes.

The adrenal glands revealed a partial pressure atrophy of the cortical portion. The capsule was intact. All 3 zones were narrowed. The entire adrenal medulla was replaced by exactly the same type of tumor cells which were present in the sulcus tumor. Necrosis as well as lymphocytic infiltration was in evidence (Fig. 4).

The peritoneal implants also revealed the exact type of tumor found in the sulcus mass.

The kidneys revealed no evidence of tumor growth. The glomeruli and their Bowman's capsules were entirely without pathologic change. The tubules showed a slight amount of cloudy swelling.

Discussion. The clinical syndrome described by Pancoast included (1) pain in the shoulder region often radiating down the arm and eventually into the fingers, (2) Horner's syndrome, (3) local destruction of the first 2 or 3 ribs, and (4) atrophy of the muscles of the hand. The Roentgen observations were described as a small, sharply defined, soft tissue shadow in the apex of the thorax which usually appeared insignificant when compared with the symptoms of the patient. Accompanying this is a destruction of one or all of the upper 3 ribs in

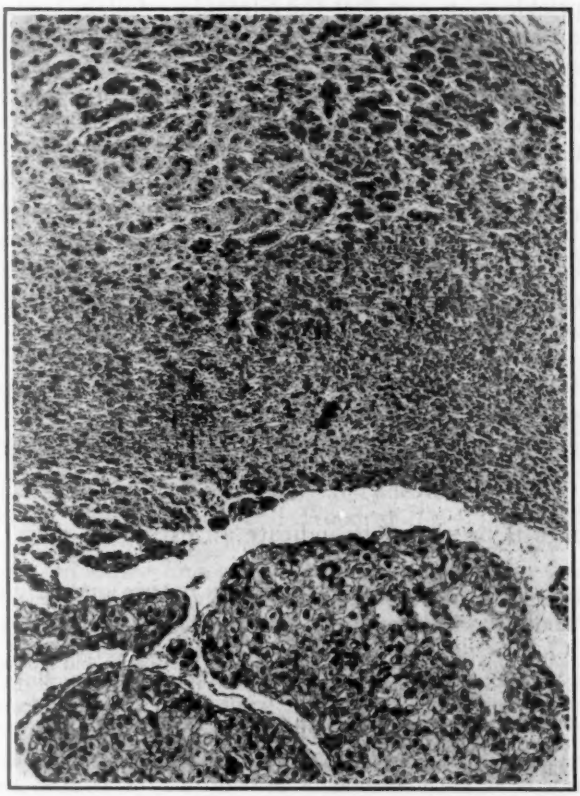


FIG. 4.—Tumor cells replacing adrenal medulla and compressing adrenal cortex. (× 150.)

their posterior aspects and the adjacent transverse processes and sometimes slight vertebral erosion.[16]

An important feature in most of the reported cases has been the absence of signs or symptoms of pulmonary disease. Most of the tumors have occurred in men and, regardless of their origin, the life expectancy is 1 year or less.[15]

The syndrome described by Pancoast was present in this case. The clinical course from the onset of pain to death was extremely rapid, totaling only 3½ months. Physical signs and symptoms of a pulmonary lesion which usually have been strikingly absent in the reported cases were present in this case, apparently due to the large size of the

tumor. The rapid growth exhibited by this lesion by Roentgen examination is also somewhat unusual. It is also worthy of note that none of the Roentgen examinations demonstrated evidence of osseous erosion.

The tumor mass in the pulmonary sulcus at postmortem examination was undoubtedly extrapulmonary and was so proven by microscopic sections. Dr. McFarland, who made a diagnosis of spinocellular carcinoma in one of Pancoast's cases, reviewed the histologic sections of this patient. He expressed the opinion that this tumor was composed of cells which are squamous epithelial cells but did not reach the prickle stage and that the adrenal medullary tumors and the sulcus tumor were the same cell type. The unusual amount of necrosis in the tumor is evidence of its rapid growth. This feature had also been noted by Barton[1] in his case. The finding of a similar type of tumor cell in both the adrenal medullas, as did Jacox,[10] raises the question of a possible adrenal medullary or sympathetic ganglion origin. Was this tumor primary in the pulmonary sulcus or in the adrenal?

From the history obtained, it is not possible to state whether the Horner's syndrome preceded the onset of scapular pain or whether it followed the onset of pain. This thought is projected with the idea that perhaps those tumors which are not bronchogenic carcinomas do arise in the precervical sinus or the cervical sympathetic ganglion Therefore, the primary origin of this tumor cannot be definitely established and Pancoast's theory of an origin from the precervical sinus deserves careful consideration.

Summary. 1. A case is reported which illustrates many of the features originally described as representing the superior pulmonary sulcus tumor.

2. Evidence is presented to indicate an extrapulmonary origin for this tumor.

3. Controversial evidence regarding the nature and origin of these tumors is briefly discussed.

I am indebted to Drs. Erwin D. Funk, George W. Chamberlin and Howard U. Miller for permission to publish the case presented and for their assistance in the preparation of this paper.

REFERENCES

1. Barton, E. M.: J. Am. Med. Assn., **111**, 515, 1938.
2. Bartstra, D. S., and Fortainer, A. H.: Cited by W. C. Hall, Am. J. Roentgenol., **44**, 838, 1940.
3. Breslin, L. J.: Canad. Med. Assn. J., **44**, 56, 1941.
4. Browder, J., and DeVeer, J. A.: Am. J. Cancer, **24**, 507, 1935.
5. Fried, B. M.: Am. J. Cancer, **23**, 247, 1935.
6. Frost, T. T., and Wolfsaw, S. E.: Am. J. Cancer, **26**, 483, 1936.
7. Gitt, J. J., and Trowbridge, E. H., Jr.: J. Missouri State Med. Assn., **35**, 405, 1938.
8. Graef, I., and Steinberg, I.: Am. J. Roentgenol., **36**, 293, 1936.
9. Hall, W. C.: Am. J. Roentgenol., **44**, 838, 1940.
10. Jacox, H. W.: J. Am. Med. Assn., **103**, 84, 1934.
11. Karsner, H. T., and Weston, P. G.: Am. J. Path., **10**, 693, 1934.
12. McFarland, J. L.: Personal communication with Dr. Erwin D. Funk.
13. Moersch, H. J., Hinshaw, H. C., and Wilson, I. H.: Minnesota Med., **23**, 221, 1940.
14. Moschcowitz, E.: J. Mt. Sinai Hosp., **3**, 198, 1937.
15. Owen, D., Hewer, T. F., and Whitaker, P. H.: Brit. Med. J., **4069**, 1360, 1938.
16. Pancoast, H. K.: J. Am. Med. Assn., **99**, 1391, 1932.
17. Sperling, S. J., and Yaskin, J. C.: Arch. Neurol. and Psychiat., **30**, 694, 1933.
18. Stein, J. J.: J. Am. Med. Assn., **111**, 1612, 1938.

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF
CARY EGGLESTON, M.D.
ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE
NEW YORK CITY
AND
HARRY GOLD, M.D.
CORNELL UNIVERSITY MEDICAL COLLEGE, DEPARTMENT OF PHARMACOLOGY
NEW YORK CITY

PENICILLIN

A Review of the Literature Through 1943*†‡

By Lieut. G. F. Schmitt, M.C., U.S.N.R.
SAN FRANCISCO, CALIF.

Factors inhibiting bacteria have been known for almost 50 years (Emmerich and Low, 1899),[45] (Emmerich and Saida, 1900).[46] The considerable literature that has arisen concerning the antagonistic relations of microörganisms has been completely and adequately reviewed by Waksman (1941)[124] and Waksman and Woodruff (1942).[125] However, only during the last several years has the general interest of the profession in the subject—primarily due to the advent of penicillin—been aroused. While the span of life of penicillin has been short, over 100 articles dealing with it have been published. Some of these are in journals inaccessible except in the larger libraries. Accordingly, the purpose of this paper is to collect and summarize the knowledge of penicillin up to the present time. Unless some articles have been overlooked unintentionally, the present bibliography is complete to January 1, 1944.

Historical. Fleming (1929)[48] observed that the growth of certain bacteria was inhibited by the chance introduction of a mold into culture plates containing bacteria. Because the genus to which this species of mold belonged was so widespread in all sorts of decaying matter, such a discovery was not remarkable. The mold, tentatively identified as *Penicillium rubrum*, was a member of the great company that rotted fruit, vegetables, meat and grain, and invalidated many kinds of biologic experiments. Such organisms were so conspicuous in all sorts of stale decaying matter that they constituted the common conception of "mold."

* Written as part of graduate work at Stanford Univ. Medical School and was made possible by the facilities of the Lane Medical Library. Dr. A. L. Bloomfield gave suggestions and advice.

† The opinions and assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

‡ This article is appearing in briefer form in the U. S. Naval Bulletin for the use of men overseas.

The year following Fleming's discovery, Thom (1930)[119] in a comprehensive monograph stated that outside of the ripening effect upon Camembert and Roquefort cheeses, the possibilities of usefulness of the Penicillia —a group of hyphomycetes which produced conidial fructifications in the form of a brush or broom (L. Penicillus, penicillum, pencil, so named in allusion to the tufts at the ends of the conidiophores)—remained unknown. The utilization of such an agent seemed to be confined to the laboratory, as Fleming (1930)[53] (1932)[49] reiterated the fact that penicillin had remarkable antibacterial properties and was useful in isolating bacteria one from another. At the same time, he, as well as Clutterbuck (1932),[22] identified the mold as *Penicillium notatum* Westling. Later, Reid (1935)[105] investigated a large number of hyphomycetes, and found that only Fleming's mold had any antibacterial effect.

Here the matter rested until Florey, Abraham, Chain, and others (1940)[19] (1941),[2] perhaps stimulated by the work of Dubos (1931–1940),[32–36] published comprehensive reports of their investigations of penicillin. These reports were so enthusiastic that large numbers of investigators have since been stimulated into action in this field.

The Media. Fleming[48,49] stated that the mold grew in a variety of different media, but best in trypsin digest broth. Later, Abraham[2] recommended Clutterbuck's[22] modification of the synthetic Czapek-Dox media:

Sodium nitrate ($NaNO_3$)	3.00
Potassium acid phosphate (KH_2PO_4)	1.00
Potassium chloride (KCl)	0.50
Magnesium sulfate ($MgSO_4H_2O$)	0.50
Ferrous sulfate ($FeSO_4H_2O$)	0.01
Glucose	40.00
Distilled water, q. s.	1000 cc.

This formula was modified by McKee and Rake[88] who substituted brown sugar for glucose. Hobby *et al.*[72] reduced the amount of brown sugar to 20 gm. and made other slight changes. Foster, Woodruff and McDaniel[58a] stated that formula containing brown sugar gave the best results, but suggested doubling the amount of sodium nitrate. They made a great number of modifications in the basal media, but failed to find any noteworthy improvement. However, ferrous sulfate and potassium chloride could be eliminated entirely, and the quantity of potassium and phosphate lowered considerably without reducing the penicillin-productive power of the mold. Kocholaty[80] substituted manganese for iron, and others[58a] stated that the addition of zinc was helpful. The use of lactose (5%) was effectual in increasing antibacterial titer for some but not for others.[58a] Challinor buffered the media more by the addition of mono- and dihydrogen phosphates.[20]

Lately, Taylor[117] compared the growth of *P. notatum* upon Czapek-Dox synthetic medium, Difco stock heart infusion broth, and Amigen (a trade name for a product consisting of an enzyme digest of purified casein and pork pancreas in which the proteins were hydrolyzed to 75% di- and tripeptides). According to him, the growth was far better on Amigen than on any other substrate.

Growth. Only known identified strains of the highest potency were selected, and these were rigidly controlled to prevent degeneration.[58,104a] The number of vegetative transfers was reduced to a minimum. A convenient method of keeping cultures at a high level was by allowing sporulation of the mold, mixing the spores with dry sterile sand, and drying

the mixture at low temperature as needed. Spores from this master race were sown upon suitable media. Frequently, the mold was grown first upon a slope of Sabouraud's media, from which a spore suspension was made by shaking with sterile water, and implanting upon sterile media. After inoculation, the shallow medium (1.5 to 2 cc.) was not disturbed so that the growth did not conglomerate into balls.[2] A delicate fluffy growth appeared 24 hours later on the bottom of the vessel, reached the top of the solution on the 3rd day, and soon the whole surface was covered with a dry mycelium which began to turn green almost immediately. By the end of a week, the growth consisted of a compact continuous wrinkled dark green felt whose upper surface containing yellow spores could not be wetted with water. Later, the mold became faded and gray. The substrate gradually turned yellow during this period of growth from a pigment, chrysogenin, which had no antibacterial action.[22] However, penicillin of high assay value was rarely found in the absence of this pigment.[58a]

The mold flourished at 22° C. (range 20° to 26°), but failed to grow at 37° C. Growth occurred over a wide range of oxygen tensions, but not anaërobically.[2] The production of penicillin was, in part, dependent upon the reaction of the media.[2,58a,117] The reaction began at the neutral point, reached pH 3 at the end of the 3rd day, gradually rose to pH 5 to 6, and finally, as the color of the mycelium faded, became alkaline. The production of penicillin was maximum slightly below the neutral point.

Yield. Usually the yield was 2 to 4 (rarely 6 to 8) Florey units per cc. of culture fluid.[2] As noted above, changes in the culture media made some difference in the amount of penicillin. Certain strains produced more penicillin than others.[58a,65,88] Challinor[20] decreased the time required for maximum production from 10 to 15 days[22] down to 5 to 6 days by the addition of 0.1 to 1 cc. of media from a previous batch to 200 cc. of the current substrate. McKee and Rake[88] found that while highly active filtrates were obtained in 10 days after original inoculation, reflooding the used fungus with fresh media caused a maximum concentration of penicillin within 6 to 7 days. There was no relation between the size of the thallus and the antibacterial titer.[117]

Parasites on the Mold. Dobbs,[30] in emphasizing the importance of keeping the culture media sterile, stated that Piptocephalus was parasitic on *P. notatum.*

Large-scale Production. While the method of growing the mold in shallow media described above is of historical interest, almost all manufacturers now use a modification of the technique described by Clifton.[21a] He constructed a tube containing a column of wood shavings 4½ feet long. The top of the apparatus contained two holes, one for the passage of culture media (Czapek-Dox containing 4% glucose and 0.1% Difco yeast extract) and the other for the admission of a stream of air. After the column was sterilized by steam, the shavings were wet with culture media, and *P. notatum* was introduced. The medium was allowed to flow at the rate of 600 to 800 ml. daily. While the prevention of bacterial contamination was a problem, it was not insurmountable, and it was believed that this method offered the best possibility for the production of penicillin in large quantities.

Penicillin. Extraction and Purification. Penicillin was obtained primarily from the substrate, but a small amount was found in the thallus.[113] The most detailed account of the production of penicillin was recorded by Abraham, Chain, Florey and others[2,5] as follows: The filtered, chilled

(40° C.) culture fluid was acidified with 10% phosphoric acid to pH 1.9, and extracted in lots of 2 liters with an equal volume of amyl acetate. The solution (in 2 liter lots) was mixed with 400 cc. of water; N/30 baryta water gradually was added to bring the pH to 6.2. The resultant deeply-pigmented red-brown solution was filtered, and treated with animal charcoal. The mixture was filtered, chilled to 4° C., and one-third volume of cold ether was added. The watery layer, acidified to pH 1.9 with 10% phosphoric acid, was extracted with vigorous shaking. Three extractions done in this manner were followed by passage through an alumina column 50 cm. long, with the formation of the following chromatogram:

(1) Dark brown layer—containing small amounts of penicillin.
(2) Light yellow layer—containing bulk of penicillin.
(3) Orange or lemon yellow layer—containing small amounts of penicillin.
(4) Purple layer—containing no penicillin.

The second fraction separated mechanically from the others was eluted 4 times with M/15 phosphate buffer (pH 7). The combined yellow eluates were extracted thrice with ether at pH 2. From this, the penicillin was returned to aqueous solution by adjustment to pH 6 with N/30 baryta water. The inactive pigment remained in the ether layer. The active substance was again extracted with ether, and the solution was passed through another alumina column. The same layers were obtained but only the second fraction was used. The process of purification was repeated as above.

The next step was reduction with aluminum amalgam, following which the solution was cooled to 4° C. and extracted with amyl acetate. The amyl acetate was then extracted with water at pH 7. The aqueous solution was reëxtracted at pH 2 at 5° C., and passed through an alumina column. This time only 3 fractions were obtained:

(1) Very light brown.
(2) Almost colorless.
(3) Greenish yellow.

Division of the column was facilitated by observation in ultra-violet light, because the first and third fractions were fluorescent. The penicillin was eluted from the second fraction with phosphate buffer. After 2 further chromatographic adsorptions from amyl acetate, the resulting column was almost colorless and homogenous. Elution with phosphate buffer, extraction with amyl acetate, and reëxtraction with N/30 baryta water at pH 5 yielded on lyophilic drying a faintly yellow barium salt of penicillin with an activity of 500 units per mg. Dawson, Meyer and others[28,90] adjusted the culture media to pH 3–4, saturated it with ammonium sulfate, and extracted the product with chloroform. The active agent was removed by phosphate buffer at pH 7.2. Extraction with chloroform and buffer was repeated, and less acidic pigments separated from most active fraction by chloroform extraction at different acidities. The penicillin was obtained as a free acid by precipitation from petroleum ether or as ammonium salt by saturation of a chloroform-benzol solution with dry ammonia gas. According to Catch, Cook and others[18,23] the most satisfactory method was by chromatographing from an organic solvent upon a column consisting of a water-retentive support (silica gel) associated with an organic base such as a hydroxide or carbonate of alkali or alkaline earth metal. The latter was applied either in the form of a dilute solution in water or was precipitated on a carrier before use. The penicillin

was extracted primarily on the relative strengths of the component acids of the media.

Properties. Penicillin has been obtained in the form of a free acid and the salts of barium, potassium, sodium, ammonium calcium, silver and strontium.[2,3,5,8,28,54,55,70a,90] Penicillin is partially soluble in ether at pH 7.2, completely soluble at pH 2, but insoluble in alkaline solutions.[22,48] It is freely soluble in water, weak saline solution, alcohol, ethyl acetate and dioxan. Penicillin is less soluble in benzene, chloroform and carbon tetrachloride. The salts are hygroscopic, the barium salt less so than the others. All rapidly lose their activity on exposure to air. The strongly dibasic acid is extremely unstable, probably from the lability of free carboxyl groups.[5] Penicillin, in the form of the acid or its salts, is easily oxidized by potassium permanganate and hydrogen peroxide, but is less sensitive to reducing agents. It is unstable toward dilute acids, alkalis, various heavy metal ions[5] and moist organic bases such as aniline, methyl aniline and dimethyl aniline. Penicillin may be treated for 1 hour at 56° C. or boiled for a few minutes without loss of activity; autoclaving at 115° C. for 20 minutes completely destroys it.[48] Penicillin does not reduce Fehling's solution, but the blue color changes to green from formation of complexes. The barium salt is strongly dextro-rotary,[6] but the strontium salt is optically inactive.[18]

The empirical formula has been suggested by Abraham and Chain,[4,5] who analyzed the dried barium salt with the following results: C—44.3, H—4.85, N—4.13, C—Me 11.6, Ba—22; no phosphorus, sulfur, or O Me; no easily reducible double bonds. From this, they suggested the formula of $C_{23}H_{30}O_{10}N_2Ba$(M.W. 640–645) or $C_{23}H_{30}O_9N_2$. A formula containing C_{25} was not excluded. These formulas agree essentially with that ventured by Catch, Cook and Heilbron:[18] $C_{23}H_{34}O_{11}NSr$. Some steps have been taken towards establishing the structural formula by Holiday.[75] From spectographic examination (maxima at 247 and 300 micra), he suggested the possible characteristics: polysubstituted hydroaromatic ring; acidic groups, probably carbonyl; and possibly the presence of a trisubstituted $\alpha\beta$ unsaturated ketone group.

The molecule has been ruptured by Abraham[4] and Catch.[18] Apparently, the following substances were formed:

(1) Carbon dioxide.
(2) Colorless water-soluble acid, which on further hydrolysis gives rise to a simple peptide.
(3) Yellow insoluble pigment ($C_{16}H_{20}O_6$ or $C_{16}H_{18}O_5H_2O$).
(4) Acetaldehyde.

Assay. A completely satisfactory method of assay is not available at the present time. A need for the establishment of a suitable method is pressing, particularly for the determination of antibacterial titer of penicillin in the substrate of the culture. Foster[57] formulated the requirements of a suitable assay: no pretreatment, accuracy, results available shortly, readings unequivocal, and the demonstration that only one penicillin is present.

The various methods may be classified under one of the following basic principles:

1. *Oxford Cup.* The progenitor of this method was that of the hole or agar cup technique described by Fleming.[48,52] Florey *et al.* modified the method by implanting tiny glass or porcelain cylinders containing penicillin in nutrient plates heavily seeded with *Staphylococcus aureus*. The

plates were incubated for 12 to 16 hours at 37° C., and the surrounding zone of bacterial inhibition read. A standard solution produced an average zone of inhibition of 24 mm., which was defined as a Florey (Oxford) unit. While keeping the basic technique, Foster and Woodruff[56a] introduced an important modification. They stated that since attempts to stabilize cultures of *S. aureus* were fraught with difficulty, a sensitive strain of *Bacillus subtilis* was substituted. They found that not only were there larger zones of inhibition, reducing the percentage deviation of error in measuring them, but also the zone edges were knife sharp, with the growth of organisms standing in clear contrast to the zone of inhibition. Recently, Dowdy and the Vincents[31] substituted paper disks saturated with penicillin for the cylinders.

2. *Serial Dilution.* This was done in tubes containing nutrient broth or upon agar plates. The essential points of the plate method were as follows: various amounts of the sample were mixed with 10 cc. melted agar, which after solidification, was streaked with a test organism. The plates were incubated overnight, and the concentration which inhibited the growth was read.

A popular technique was titration in liquid broth. Fleming[52] used a broth consisting of peptone (1 gm.), sodium chloride (0.5 gm.), glucose (1 gm.), Andrade's indicator (1 cc.) and water (q. s. to 100 cc.). A 3 mm. loop from a 24 hour broth culture of *S. aureus* was inoculated into 5 cc. of the media. Serial dilutions of penicillin were made, and added to the broth. After incubation for 24 hours, the end-point was the appearance of a red color in the media. From a comparison between a known standard and the unknown, the latter was calculated.

Rammelkamp[97] tested the susceptibility of a number of organisms to the action of penicillin. Hemolytic streptococci were found to be 4 to 16 times more sensitive to penicillin than staphylococci, and hence these organisms were to be preferred. The test organism was a 12 hour broth culture of a Group A strain of hemolytic streptococci, which was inoculated into veal infusion broth containing 1% erythrocytes. This was diluted so that the final number of organisms varied between 1000 and 10,000 per cc. Two series of tubes were set up: one for the unknown and the other for the control. The latter contained 20 Florey units per cc. of 0.85% normal saline solution. Serial dilutions were made in the accepted manner, incubated for 18 hours, and the tubes were then examined for hemolysis. The end-point was usually clear, but as a check for sterility, the contents of the tubes on both sides of this point were streaked upon a blood agar plate. Calculations made from comparison of the end-points of the unknown and control gave the concentration of the drug in the unknown solution.

Hobby, Meyer and Chaffee[72] modified the method slightly by using a standard strain of hemolytic streptococcus (C 203 M). Their end-point was the failure of a given dilution of penicillin, culture media and erythrocytes to develop turbidity after 24 hours. They reported the activity of penicillin as the number of micrograms necessary to inhibit the growth of 2 to 4 million hemolytic streptococci. Recently, Wilson[126] described a test based upon the inhibition of hemolytic streptococci using 5% washed sheep cell suspension as an indicator. She stated the results could be read within 4 hours.

Since the Florey (Oxford) unit as defined above did not apply to the serial dilution method, Florey and Jennings[54] defined this unit in terms of the latter as follows: A unit is that amount of penicillin which when dis-

solved in 50 cc. of meat extract broth completely inhibits the growth of a test strain of *S. aureus*. Expressed differently, a meat extract broth containing 1 unit of penicillin per mg. just inhibits the growth of *S. aureus* in dilutions of 1 to 50,000.

3. *Turbidimetric.* Foster *et al.*[56,57,58] stated that the inhibition of growth of a culture of *S. aureus* in liquid media was a function of the penicillin concentration, and that the turbidity of the mixture as measured by a colorimeter was in inverse ratio to the strength of the penicillin. Recently, the technique was modified by the substitution of *B. adhærans* for *S. aureus*. The time required for an end-point was reduced to 3 to 5 hours. This method was peculiarly suitable for use in assaying substrates.

4. *Other Methods.* Foster and Wilker[58] described assays with which they had little success:

(1) Methylene blue reduction of washed cells of susceptible organisms.
(2) Inhibition of luminescence in cultures of luminescent bacteria.
(3) Microscopic observation of cessation of motility of bacteria.
(4) Microscopic observation of the appearance of enlarged or involuted cell shapes.

5. *Titration of Acid Formed by Lactic Acid Bacteria.* As noted above, the ideal method of assay has not been suggested. However, the easiest and most practicable for routine use is the technique of serially diluting the penicillin in tubes containing broth, test organism and erythrocytes. However, this as well as the other methods, has disadvantages, which Foster and Woodruff[57] have summarized:

(1) *Oxford Cup.* (*a*) Affected by the pH of the media. (*b*) Organism and penicillin must be inoculated within a very short time of one another. (*c*) The presence of a halo may make reading of the end-point difficult.
(2) *Serial Dilution* (*Liquid Broth*). (*a*) Sterile samples are necessary or else sterility is effected by passage through a Seitz filter. (*b*) End-point may not be definite.
(3) *Serial Dilution* (*Plate Method*). (*a*) Affected by changes in pH. (*b*) Presence of bacteria containing penicillinase may affect end-point. (*c*) Tedious.
(4) *Turbidimetric.* (*a*) Large quantity of sample necessary. (*b*) Too difficult for routine use.

Relatives of Penicillin. In the literature one finds the names of related and degradation products of penicillin. It is impossible to predict which, if any, are identical, which will be discarded, or what new substances will be added subsequently.

Penicillin B. Roberts,[108] Van Bruggen[123] and others isolated a substance which they called penicillin B to differentiate it from the original penicillin of Abraham. The first report stated that this compound was readily separated from the culture media by adsorption upon benzoic acid, and purified by repeatedly dissolving in acetone. Subsequent reports stated that penicillin B was better extracted by precipitation with uranium acetate, centrifuging and siphoning off the supernatant fluid. The latter was washed with water, and extracted with a volume of 0.2 M phosphate buffer sufficient to give the mixture a creamy consistency. After standing for several hours, the mixture was centrifuged, reëxtracted, and finally salted out with ammonium sulfate. Penicillin B occurred as a light yellow readily-soluble powder, which gave positive tests for protein. Study suggested that it was a flavo-protein of enzyme nature. It was lethal to both Gram-negative and positive organisms, but the presence of glucose

was necessary for its antibacterial action. The glucose was oxidized ($R.CHO + H_2O + O_2 \rightarrow R.COOH + H_2O_2$) with the formation of hydrogen peroxide, to which antibacterial action was attributed. Unfortunately, penicillin B was toxic to mice, although non-cumulative; attempts to detoxify it were unsuccessful.

Penatin. Kocholaty[79,80,81] stated that certain strains of penicillin differed not only in the rate of production of penicillia, but also in the compounds produced. He isolated a substance called penatin, and prepared it by adsorption with kaolin at pH 4, elution of the washed kaolin with pyridine or sodium phosphate at pH 6.3, followed by precipitation with dioxane. The product was dissolved in water, then dried by the lyophilic method. Penatin was a yellowish hygroscopic powder completely soluble in water. While it was sensitive to alkalies, it was more resistant to acids. Penatin far surpassed penicillin not only because it was bacteriostatic in dilutions of 1 to 400 millions, but also because it was antagonistic to certain Gram-negative organisms (*E. coli* and *Brucella abortus*).

Notatin. The co-workers of Coulthard[25] isolated a substance prepared by concentrating the culture filtrate to one-fifth its volume under mild conditions, and precipitating the concentrate with acetone or tannic acid. In the latter case notatin was extracted from tannic acid with acetone. Regeneration of the crude substance was effected from complexes formed with tannic acid or Reinecke's salt. Notatin was a buff-colored powder freely soluble in water, but insoluble (6.7%), nitrogen (11.8%) and phosphorus (0.58%). It exhibits many of the reactions of protein, and has a molecular weight of 73,000. Since it has absorption spectrum maxima of 280, 375 and 465 mr, it is classified as a yellow enzyme. Notatin, an aërodehydrogenase, executes its activity only under certain well-defined conditions: presence of oxygen and glucose and the absence of appreciable amounts of catalase. Its antibacterial activity may be due to the liberation of hydrogen peroxide.[14a] The best preparations completely inhibit the growth of *S. aureus* in dilutions of 1 to 1 billion, and it is active against *Streptococcus hemolyticus, Diplococcus pneumoniæ, Eberthella typhosus* and *paratyphosus, Vibrio cholera, Bacillus anthracis* and *B. proteus vulgaris.*

Comparison of Penicillin B, Penatin and Notatin. Birkinshaw and Raistrick,[14a] Foster[58a] and others pointed out that these 3 substances were probably identical, and that their formation was dependent upon the pH of the media. Normally, using materials inherently impure containing traces of heavy metals (zinc, copper, manganese) or organic supplements (yeast extract), the pH underwent normal variations. However, extremely pure ingredients effected no secondary rise in the pH which remained at pH 3.4. It is at the latter ranges that the above substances are formed, and it accounts for the presence of notatin (penatin, penicillin B, coli factor of Waksman and Woodruff[125]) in many cultures of *P. notatin.* In a word, notatin is formed in acid media, while penicillin is produced in neutral media. It is possible that different strains vary in the production of each.[58a] Of the substances isolated, notatin seems to hold the most promise, for it adds a number of organisms to the growing list of those adversely affected by products of the growth of *P. notatum.*

Penicidin. This was reported by Atkinson,[10,11] who noted that a certain penicillum (mold 9) produced a substance which was inhibitory to Gram-positive and negative organisms. The mold grew on a modified Czapek-

Dox media at 18° to 20° C. for 5 days, after which the active component was removed by concentrating the substrate *in vacuo* to one-tenth its original volume, filtering, adjusting to pH 7, and extracting with ether for several hours. The ether extract was washed with water, adjusted to pH 4, and the penicidin was removed by dilute acid. The reaction was changed to neutral, the material was reëxtracted with ether and evaporated *in vacuo* to a small volume. The addition of petroleum ether caused an immediate precipitate which on standing in the cold settled out as a pale yellow oily layer of incompletely purified penicidin. Penicidin was relatively heat-resistant; not readily destroyed by hydrochloric and sulfuric acids; easily inactivated by potassium and barium hydroxides; soluble in chloroform, benzene, ether, ethyl alcohol and dilute mineral acids; and insoluble in petroleum ether. Penicidin was active against *Eberthella typhosus* in dilutions of 1 to 100,000.

Penillic Acid. Duffin and Smith[37] and Oxford, Raistrick and Smith[93a] reported that highly active penicillin preparations kept at pH 2 exhibited a rise of optical activity, which, after reaching a maximum, remained constant. Following this phenomenon, only part of the penicillin previously extractable by ether could be obtained. The remaining substance, a constituent of the molecule of penicillin, was strongly dextro-rotatory $\left(\frac{A}{B} + 600\right)$. The acid, which when in solution had a pale blue fluorescence in ultra-violet light, crystallized from water in brilliant rhombo or hexagonal plates. It had some of the properties of amino acid, and it did not give a blue color with ferric chloride—a characteristic of penicillamine.

Penicillamine. This was obtained by Abraham, Chain *et al.*[6] by hydrolyzing barium penicillin at 100° C. for 1 hour by N/10 sulfuric acid. The base thus recovered was precipitated from a concentrated solution by bichloride of mercury. After demercurizing with hydrogen sulfide and evaporation at room temperature under diminished pressure, a mass of homogenous crystals (penicillamine) was obtained. Penicillamine had the formula of $C_6H_{11}O_4N \cdot HCl(C_6H_{12}O_6 + NH_3 - 2H_2O)$, was optically inactive, and seemed to be an integral part of the penicillin molecule. The nitrogen was in the form of an amino acid group, although not typical of an alpha-amino acid. Among its other properties, it gave a deep blue color with ferric chloride, reduced ammoniacal silver nitrate on gentle warming, and produced a green color with Fehling's solution. The exact significance of this degradation product was unexplained.

Esters. Although Abraham and Chain[5] were unsuccessful in their attempts to esterify penicillin by the action of various alkyl iodides on the silver salt, this did not deter Meyer *et al.*[91,92] who successfully prepared methyl, ethyl, n-butyl and benzohydryl esters by letting the free acid of penicillin react with the corresponding diazo compound. The ethyl and normal butyl esters appeared to be stable and were not destroyed by acids.

Antibacterial Actions. *Susceptible and Naturally-resistant Organisms.* Fleming[48] noted that penicillin acted best against pyogenic cocci and the diphtheria group while Gram-negative bacilli were insusceptible. Susceptibility occurred in a 1% solution; or, if the organism were resistant, did not take place in a 10% solution. The first use of penicillin was a laboratory aid to prevent the growth of more robust organisms in a

mixed culture.[26,51,53] In fact Fleming (1932)[49] stated penicillin's main uses were:

(1) To isolate hemophilic bacteria such as *B. pertussis* and *B. influenzæ* from streptococci and pneumococci.
(2) Isolation of one partially insensitive microbe in pure culture from a mixture of more sensitive organism (acne bacillus from staphylococci).
(3) Separation of Gram-negative cocci from other mouth organisms.
(4) Demonstration of bacterial antagonisms.

The chief use, then, of penicillin was as a laboratory aid until the work of Abraham, Florey *et al.*[2] resulted in the impetus necessary to use the drug in man. Since then, lists of organisms against which penicillin was found to be active have been published by several authors;[2,48,88] but the list usually referred to is that of Dawson *et al.*[28] and Hobby, Meyer and Chaffee,[72] which summarized the susceptible and resistant organisms:

Susceptible	*Insusceptible*
Pneumococcus	*Hemophilus influenzæ*
Strep. hemolyticus	*B. coli*
Staphylococcus	*B. typhosus*
Meningococcus	*B. dysenteriæ*
Gonococcus	*B. proteus*
Strep. viridans	*B. paratyphosus A*
B. subtilis	*B. enteritidis*
Clostridium welchii	*B. pyocyaneus*
Vibrion septique	*B. fluorescens*
Clostridium histolyticus	*B. prodigiosus*
B. sporogenes	Friedländer's bacillus
B. ædematiens	*S. albus*—1 strain
B. sordelli	*Micrococcus albus*—1 strain
Lactobacillus	*Monilia albicans*
Cryptococcus hominis	*Monilia kruzei*
	Monilia candida

Certain strains of *Actinomycosis bovis* were reported to be susceptible by Abraham and Chain[2] and by Herrell.[67] Kocholaty[79] stated that penicillin had a weak action against *B. abortus*. Hobby, Meyer and Chaffee[73] made a study of the relative susceptibility of pneumococci, streptococci and staphylococci by determining at intervals the number of survivors in a standard solution of penicillin. They found that resistance increased in the order named.

Bornstein[17] stated that 27 strains of enterococci representing Sherman's 4 types and 6 strains of *S. lactis* were resistant. *Mycobacterium tuberculosis* was resistant according to Abraham and Chain,[2] Herrell,[67] and Robinson.[110] The fact that certain organisms were susceptible and others were not stimulated Abraham and Chain[1] to investigate this problem. They crushed *B. coli*, and produced an extract which, upon incubation at 37° C., destroyed the growth-inhibiting properties of penicillin on *S. aureus*. This extract apparently contained an inhibiting enzyme which was called penicillinase. This substance was not present in the supernatant broth from cultures of *B. coli*[72] or in cultures of *S. aureus*. Apparently, penicillin was not destroyed by penicillinase but merely inhibited its action.[2] The presence of this enzyme may determine whether an organism is normally resistant to penicillin. Recently, Harper[62b] found that the best source of penicillinase was the paracolon bacillus. The product prepared from this organism actively destroyed penicillin rather than merely causing inhibi-

tion. He suggested that the dried powder may be advantageously employed to inhibit the action of penicillin in blood cultures.

Induced Resistance. Since it was well known that organisms became resistant when exposed to sulfonamide drugs,[83a] the question arose whether bacteria became resistant to penicillin. McKee and Houck[86] passed a strain of pneumococcus (Type III) through broth containing an amount of penicillin which first permitted growth. After 26 consecutive passages, the culture became resistant to 10 times the greatest amount of penicillin which previously permitted growth; after 55 passages, 30-fold more resistant. Increase in resistance was associated with loss of virulence in mice, which was not restored by serial passages through mice.[87] Rammelkamp and Maxon[103] stated that although growing staphylococci in increasing concentration of penicillin engendered resistance, there was a reduction in the growth velocity of the resistant strains, but no penicillin-destroying enzyme was demonstrated. Schmidt and Sesler[113] reported that the rate and degree at which resistance to penicillin developed in pneumococci varied significantly with various strains, and that established resistance was maintained for considerable periods. The development of insensitivity *in vitro* was accompanied by a similar quality *in vivo*. Schnitzer, Camagni and Buck[114] found that small colony variants (G forms) of Strain 314 of *S. albus* were induced by the action of penicillin.

Mechanism of Action. It was agreed that penicillin was bacteriostatic,[5,19] but may be bactericidal under certain conditions.[28,67,73] When sterilization of a culture did not occur, there was always a marked reduction in the number of organisms[72] according to Abraham,[2] bacteriostasis for oxygen uptake of colonies of bacteria exposed and unexposed to penicillin was the same; furthermore, staphylococci removed from the noxious effect of the drug continued to grow. Penicillin did not act like any other therapeutic agent in that it was not a detergent, not hemolytic, and was unaffected by the presence of pus, products of tissue destruction, large numbers of bacteria and para-amino benzoic acid.[2,28,50,67,72] In fact, the last-named substance enhanced its antibacterial effect on *B. subtilis*. Erythrocytes and plasma did not inhibit its action.[102] Penicillin was effective only during the multiplication of bacteria.[73] Pulvertaft[96] suggested that the effect of the drug was upon bacterial fission—not upon the metabolism and growth of the individual organism. Penicillin was not absorbed or destroyed by bacteria. With exception of staphylococci,[104] lysis of bacteria did not occur.[73] However, Gardner[59] noted certain morphologic changes, the more important of which were spherical enlargement of cells, incomplete fission, and, in the case of streptococci, increased length of chains. Even Gram-negative organisms exhibited elongation of of cells. There was no change in the structure of the meningococcus.

Comparison of Sulfonamides With Penicillin. Resistance to sulfonamides did not indicate resistance to penicillin.[24,84,94] McKee and Rake,[89] Tillett, Cambier and Harris[120] reported that strains of pneumococci resistant to sulfonamides were susceptible to the action of penicillin. Induced resistance of organisms to penicillin was acquired only after prolonged exposure, but resistance to sulfonamides was attained more readily. Fleming,[50] after studying *in vitro* the inhibitory powers of sulfathiazol and penicillin against staphylococci and streptococci, came to the conclusion that penicillin was 4 times more potent than sulfathiazol. Powell and Jamieson[95] conducted a similar experiment in mice infected with staphylococci, and found that the survival rate of the ones treated with penicillin was approximately twice of those treated with sulfathiazol in experimental ocular lesions caused by the staphylococcus.

The entire problem was well summarized by Florey *et al.*[2] who stated that while penicillin resembled sulfonamides in its bacteriostatic action, it had a number of advantages:

(1) Its action was stronger.
(2) It was influenced only to a minor extent by the number of bacteria to be inhibited.
(3) It was not hydrolyzed by hydrolytic protein products or pus.
(4) It combined low toxicity to cells with powerful bacteriostatic action.

Pharmacology. *Absorption.* Saliva did not inactivate the bitter tasting drug, but the hydrochloric acid of the stomach (not the pepsin) rapidly destroyed the active portion.[98,99] When the stomach was by-passed by a duodenal tube, penicillin was absorbed from the intestine[2,102] without damage to the living cells.[19] Rectal administration was precluded because of the destructive action of penicillinase.[1] The drug was slowly absorbed after subcutaneous injection, and there was a long delay before it appeared in the blood stream. The concentration did not reach the levels attained when it was given intramuscularly or intravenously.[102] Intermittent intramuscular administration caused a rapid rise in the blood level, but not to the same heights as intravenous injection. The concentration tended to remain at a peak for 30 to 45 minutes. Intravenous use caused a rapid rise in the serum level, which reached a maximum immediately after injection, but then a rapid fall occurred. Traces remained for 30 to 210 minutes.[102] Absorption following introduction into body cavities was similar to the subcutaneous route.[102]

In normal subjects, penicillin was both slowly absorbed and excreted following the intrathecal injection of 5000 to 10,000 units. The absorption was more rapid in patients with meningitis.[101] Abraham and Chain[2] and Ayer[12] introduced penicillin intrasternally without harm, even the solid drug was introduced into a cerebral abscess without toxic effect.[96] Penicillin was not detected in the cerebrospinal fluid following intravenous administration.[102]

Blood. Although elevated temperatures inhibited penicillin, it was unlikely that the hyperthermia caused by febrile diseases caused any significant loss during the short time the drug remained in the body. Rammelkamp and Keefer[102a] reported that the degree of antibacterial action was proportional to the concentration of penicillin in the serum. Maximum effects against hemolytic streptococci were produced by concentrations of 0.019 to 0.156 Florey units per cc. of serum. Concentrations of at least 0.156 units were required for maximum bacteriostasis against *S. aureus.* A suitable level was more easily maintained by the frequent injections of smaller amounts rather than the use of larger amounts less often.[28]

The action of penicillin upon leukocytes is a topic of importance, for it is upon these, after bacteriostasis was produced, that the ultimate destruction of bacteria depends.[2] Florey[48] reported a fall of total leukocytes with a relative decrease in the neutrophils during the first 24 hours of the drug's administration in mice; but a regeneration was noted within 48 hours.

White blood cells, as recorded by Abraham,[2] were killed immediately in concentrations of penicillin of 1 to 100; 50% immobilized in dilutions of 1 to 250; and unharmed 1 to 500. This confirmed the earlier work of Fleming[48] who reported leukocytes were unaffected in penicillin solutions of 1 to 600. Leukocytes remained active in any concentration reached after intravenous administration. Penicillin did not penetrate erythrocytes,[102] cardiovascular and respiratory systems. Except for transient reversible depression of a cat's heart upon perfusion with penicillin solu-

tions (1 to 5000),[61] there was no effect on these functions within limits of therapeutic dosage.[19]

Kidney. Slight evidence of tubular damage was reported in rats.[19] Occasionally, in man, there was a slightly elevated blood urea (to 35 mg. per 100 cc.) unassociated with albuminuria during the administration of penicillin. Withdrawal of the drug caused a return of the urea to normal. Turner[121] explained this curious fact as possibly caused by the inhibition of urease by penicillin.

Excretion. Some penicillin was destroyed in the body[99]—possibly in the liver—but the exact location remains unknown. Incubation with slices of liver, kidney, spleen, muscle and so forth caused no noticeable destruction.[2,102] The small amount of inactivation was related to the short time the drug stayed in the body. Rammelkamp and Keefer[102] estimated that 37 to 99% of the quantity administered was excreted unchanged—principally within an hour—in the urine. An excretion rate of 50% was considered to be an average figure.[19,69] An increased volume of urine aided in the elimination of penicillin.[102] Renal failure delayed excretion with a consequent rise in the concentration of penicillin in the blood.[102] Rammelkamp and Bradley[98] suggested that the rapid excretion was caused by the passage of the drug through the renal tubules as well as the glomeruli. The administration of diodrast—known to be excreted by the tubules—decreased the loss of penicillin. The addition of such substances as hippuran or phenol red may retard the elimination of penicillin by blocking the tubules.

Toxicity in Animals. Hobby, Meyer and Chaffee[74] stated that the L.D. 50 dose for an 18 gm. mouse was 32 mg. of the sodium salt. They pointed out that a cardinal symptom of toxicity was respiratory embarrassment—choking, gasping, rapid respiration. The presence of the pulmonary phenomena following toxic doses (30,000 F. U. [0.5 gm.] per kg.) into mice was confirmed by Robinson.[110] Hamre *et al.*[62a] reported that the acute toxic dose to mice, rabbits and guinea pigs was low—about 100,000 units (1 gm.) intravenously. The last-named animal was more sensitive to large doses of subcutaneous penicillin, than the other two, but within the limits of therapeutic doses (100 units per kg.), none of the animals was harmed. There was little doubt that the doses given by various investigators were large, and it was generally agreed that penicillin was relatively non-toxic in doses far exceeding those necessary for therapeutic purposes.[28,88,110] Although a complete histologic study of tissues of animals dying of large doses of penicillin—given rapidly or over a long period of time—has been contemplated,[115] none has yet appeared. However, according to one group of authors, the pathologic change most frequently noted was pulmonary congestion.[74]

Toxicity. No deaths resulted from therapeutic dosages of penicillin. Impurities remaining after extraction were believed to be the prime causes of reactions.[41,54,110] Since the drug now used is still considerably unrefined, the elimination of foreign substances may decrease these reactions listed by Lyons:[83]

(1) Chills with or without fever after intravenous injection.
(2) Eosinophilia—20 to 30%.
(3) Burning pain at the site of an intramuscular injection.
(4) Headache.
(5) Faintness and flushing of the face.
(6) Unpleasant taste following parenteral injection.
(7) Tingling in the testes.
(8) Muscle cramps.
(9) Femoral phlebothrombosis.

Certain untoward effects may be caused by the drug itself. These were grouped by the same author as follows:

1. Urticaria: This most common complication occurred in 5.7% of his cases. The condition, benefited by epinephrine, persisted for 3 to 5 days, then disappeared. Fever to 103° F., abdominal cramps and eosinophilia were frequent concomitants. Although it was believed that this was an allergic manifestation, sensitivity tests were negative.
2. Fever in Afebrile Patients.
3. Transient Azotemia: A rise of 5 to 10 mg. of urea per 100 cc. of blood was not uncommon. Rarely did the urea concentration exceed 35 mg.
4. Thrombophlebitis: This may or may not be an inherent property of penicillin *per se*. This complication has become less frequent with further purification of the drug, use of dilute solutions, and by the daily change of the needle during the use of the continuous intravenous technique.[15] The intrathecal injection of 10,000 units, Rammelkamp and Keefer[101] reported, produced headache, vomiting, increased pressure and phagocytosis in the cerebrospinal fluids; 5000 units caused only slight headache and hyperleukocytosis of the fluid.

Administration. Penicillin is available in vacuum-packed ampules containing 5000, 10,000, 25,000, 100,000 and 1,000,000 units.[78] The drug is readily soluble in distilled water, normal saline solution and 5% dextrose. The following methods of administration have been used or are now in vogue:

1. *Oral.* Florey and Florey[55] covered 20,000 units with cellulose acetate phthallate, and found absorption was irregular. Subsequently, this technique, together with the use of the duodenal tube, was abandoned.
2. *Continuous Intravenous.* For almost all infections—particularly the severe generalized ones—this is the method of choice. The drug is dissolved in the vehicle selected at a concentration of 50 to 100 units per cc. A needle is inserted into the vein, and anchored securely. To aid in preventing thrombosis, the needle is changed frequently. Except during the patient's sleep or delirium, the extremity need not be confined. Approximately half the daily dose is connected to the intravenous apparatus morning and evening. The first 200 cc. of the solution is given rapidly, after which then is a reduction in the rate of flow to 30 to 40 drops per minute. If there is any interruption in the flow of penicillin solutions, glucose or saline solution may be substituted, thus eliminating the necessity of removing the needle. The method is without major discomfort to the patient, and conserves the time of the medical personnel.
3. *Intermittent Intravenous.* The calculated dose is administered in a solution containing 1000 to 5000 units per cc. every 3 hours.
4. *Intramuscular.* In unskilled hands, the intramuscular injection into the gluteal or deltoid muscles is best.[55,83] The solution containing 5000 units per cc. is injected every 3 hours. Some residual soreness may be eliminated by the use of saline solution instead of distilled water.
5. *Subcutaneous.* The same strength solution used for the intramuscular injection is prescribed. In both these methods, the site of injection must be changed frequently to avoid severe local reactions.[62a] Because of the rapidity of the elimination of the aqueous solutions, Hobby, Meyer and Chaffee[74] prepared homogenous pellets by grinding penicillin (1 part) and cholesterol (4 parts) as well as oily suspensions made by mixing the sodium salt in water and sesame oil. While these methods have been used in animals, they are so far impractical in man. The same group of investi-

gators[91,92] successfully combined penicillin with certain aliphatic hydrocarbons to form esters. Their activity—both subcutaneously and orally—was undoubtedly due to hydrolysis. Although the oral dose approached the toxic dose, the margin of safety of the subcutaneous route was greater. Further work is required before this method can be fitted into the scheme of things.

6. *Topical.* Penicillin diffuses poorly, hence it is used locally in wounds, infections of pleura and joint cavities and so forth. This is in addition to the other parenteral routes listed above. The powder and highly-concentrated solutions are not used because of their highly irritating properties.[21,78,110] The solution of choice is isotonic saline containing 250 units per cc.[78,83] This may be used as a spray or by immersing gauze in it. Mucous membranes of the nose or accessory nasal sinuses are unharmed by it.[16] Recently, Robinson and Wallace[109] suggested a dressing inoculated with penicillin too crude for parenteral use. Clark *et al.*[21] prepared a cream composed of lanette wax, castor oil, water and penicillin especially suitable for burns.

7. *Intraspinal.* The drug has been used in solution intrathecally,[13,96,101] intracisternally and as the solid drug directly into cerebral abscesses.[96] The exact strength of the solution to be given intrathecally has not been established. However, 10,000 units (5000 units per cc. of saline) has been injected twice daily without harm.[15]

8. *Intranasally.* Delafield and others[29] prepared a snuff composed of lycopodium (94 parts), menthol (5 parts) and penicillin (1 part). It aided in the reduction of pyogenic organisms, but was ineffectual in controlling the common cold. Sufficient clinical investigation has not been done to evaluate this type of therapy.

Bloomfield[15] pointed out that the administration of penicillin therapy in a hospital is best vested in a team consisting of physicians especially trained in the use of the drug plus the necessary technical help. This group evaluates the condition of the patient and prescribes the dose of penicillin. The preparation and injection of the drug together with the responsibility of keeping adequate records lies with the members of this committee.

Therapeutics. The expression of precise dosages is premature at the present time. With continued purification of the drug, modifications will be made. However, certain general rules have been made, chiefly by Keefer[78] and Lyons,[83] which are summarized below:

1. *Staphylococcal Infection With Bacteremia.* Although penicillin is not inhibited by toxic products, the focus of infection if surgically accessible should usually be drained. Generally, a daily dose of 200,000 to 400,000 units keeps the infection under control. As the patient improves, the dose may be gradually reduced (50,000 units a day). In assaying clinical improvement, too much regard must not be attached to the temperature chart, for lessening of pain, improvement of appetite, and a sense of well-being are equally important.[55] The total amount required may be 500,000 to 2,000,000 units given over a period of 7 to 14 days. Penicillin does not control staphylococcal endocarditis.[83]

2. *Staphylococcal Infections Without Bacteremia.* Moist dressings dipped in a solution containing 250 units of penicillin per cc. of salt solution are applied directly to the open lesions of osteomyelitis. Burns or pyogenic infections are favorably influenced by these wet dressings or a neutral cream containing penicillin.[15a,21] The treatment of empyema requires the injection of 50,000 units in physiologic saline twice daily. In all these infections, supplemental intravenous or intramuscular injections are usu-

ally necessary. Penicillin has proved effectual locally in infections of the middle ear and of the cornea.[111,112]

3. *Streptococcal Infections.* Circumscribed infections are best drained, and treated with penicillin applied locally. With the exception of the resistant viridans,[7,107] and thermophilic (fœcalis) groups, a smaller dose (100,000 units daily) inhibits this type of infection.

4. *Gonorrhea.* Mahoney and his co-workers[84] report that 10,000 units given intramuscularly every 3 hours for 15 doses cured this disease satisfactorily. Florey and Jennings,[54] Herrell[68] and others find that a somewhat smaller dose is satisfactory. It is generally considered that the injection of 100,000 to 150,000 units, using the continuous intravenous technique will cure almost all cases of gonorrhea.[15]

5. *War Wounds.* Lyons[83] and Thomson *et al.*[119a] report the largest experience to date. Because penicillin alone does not control the polymicrobial character of the wounds, surgical intervention is necessary. High concentrations of locally applied penicillin with adequate intravenous or intramuscular therapy are usually necessary. Both these excellent articles should be read in the original.

6. *Actinomycosis.* Temporary improvement has been noted and clinical trials are in the process of being carried out. Apparently not all strains are susceptible.

7. *Biliary Infections.* Since a small quantity of penicillin is excreted in the bile, the drug may be of some aid in the control of this infection.[99]

8. *Upper Respiratory Infection.* Antiseptic snuffs containing penicillin lessen the number of pyogenic organisms in the nose,[29] may have some use in the prophylaxis of diphtheria or meningitis,[38] but has no effect on the common cold.

9. *Syphilis.* Preliminary trials by Mahoney have shown that penicillin may be of some value in the treatment of early syphilis; but no extensive clinical reports are available. The correct evaluation is a long-range problem.

10. *Malaria.* This disease is not controlled by penicillin.[83]

REFERENCES

(1.) **Abraham, E. P.**, and **Chain, E.**: Nature, **146**, 837, 1940. (2.) **Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., Jennings, M. A.**, and **Florey, H. W.**: Lancet, **2**, 177, 1941. (3.) **Abraham, E. P.**, and **Chain, E.**: Nature, **149**, 328, 1942. (4.) **Abraham, E. P., Baker, W., Chain, E., Florey, H. W., Holiday, E. R.**, and **Robinson, R.**: Nature, **149**, 356, 1942. (5.) **Abraham, E. P.**, and **Chain, E.**: Brit. J. Exper. Path., **23**, 103, 1942. (6.) **Abraham, E. P., Chain, E., Baker, W.**, and **Robinson, R.**: Nature, **151**, 107, 1943. (7.) Anonymous: Am. Prof. Pharmacist, **8**, 491, 1942. (8.) Anonymous: Med. Times, **71**, xliv, 1943. (9.) Anonymous: Med. Times, **71**, xxxiv, 1943. (10.) **Atkinson, N.**: Australian J. Exper. Biol. and Med. Sci., **20**, 287, 1942. (11.) **Atkinson, N.**: Australian J. Exper. Biol. and Med. Sci., **21**, 15, 1943. (12.) **Ayer, J. B.**: New England J. Med., **228**, 422, 1943.

(13.) **Barker, L. F.**: Am. J. Med. Sci., **206**, 701, 1943. (14*a*.) **Birkinshaw, J. H.**, and **Raistrick, H.**: J. Biol. Chem., **148**, 459, 1943. (14.) **Blake, F. G.**, and **Craige, B., Jr.**: Yale J. Biol. and Med., **15**, 507, 1943. (15.) **Bloomfield, A. L.**, *et al.*: In press. (15*a*.) **Bodenham, D. C.**: Lancet, **2**, 25, 1943. (16.) **Bordley, J. E., Crowe, S. J., Dolowitz, D. A.**, and **Pickrell, K. L.**: Ann. Otol., Rhinol. and Laryngol., **51**, 936, 1942. (17.) **Bornstein, S.**: J. Bacteriol., **39**, 383, 1940.

(18.) **Catch, J. R., Cook, A. H.**, and **Heilbron, I. M.**: Nature, **150**, 633, 1942. (19.) **Chain, E., Florey, H. W., Gardner, A. D., Heatley, N. G., Jennings, M. A., Orr-Ewing, J.**, and **Sanders, A. G.**: Lancet, **2**, 226, 1940. (20.) **Challinor, S. W.**: Nature, **150**, 688, 1942. (21.) **Clark, A. M., Colebrook, L., Gibson, T., Thompson, M. L.**, and **Foster, A.**: Lancet, **1**, 605, 1943. (21*a*.) **Clifton, C. E.**: Science, **98**, 69, 1943. (22.) **Clutterbuck, P. W., Lovell, R.**, and **Raistrick, H.**: J. Biochem., **26**, 1907, 1932. (23.) **Cook, A. H.**: Biochem. J., **36**, xxiii, 1942. (24.) **Cook, E. N., Pool, T. L.**, and **Herrell, W. E.**: Proc. Staff Meet., Mayo Clin., **18**, 433, 1943. (25.) **Coulthard, C. E., Short,**

W. F., **Michaelis, R., Sykes, G., Skrimshire, G. E. H., Standfast, A. F. B., Birkinshaw, J. H.,** and **Raistrick, A. H.**: Nature, **150**, 634, 1942. (**26.**) **Craddock, S.**: Lancet, **1**, 558, 1942.

(**27.**) **Dawson, M. H., Hobby, G. L., Meyer, K.,** and **Chaffee, E.**: J. Clin. Invest., 20, 434, 1941. (**28.**) **Dawson, M. H., Hobby, G. L., Meyer, K.,** and **Chaffee, E.**: Ann. Int. Med., **19**, 707, 1943. (**29.**) **Delafield, M. E., Straker, E.,** and **Topley, W. W. C.**: Brit. Med. J., **1**, 145, 1941. (**30.**) **Dobbs, C. G.**: Nature, **150**, 319, 1942. (**31.**) **Dowdy, A. H., Vincent, H.,** and **Vincent, J.**: Unpublished. (Cited by Foster and Woodruff, Ref. 57.) (**32.**) **Dubos, R.,** and **Avery, O. T.**: J. Exper. Med., **54**, 51, 1931. (33.) **Dubos, R. J.**: J. Exper. Med., **70**, 1, 1939. (**34.**) **Dubos, R. J.**: J. Exper. Med., 70, 11, 1939. (**35.**) **Dubos, R. M.,** and **Cattaneo, C.**: J. Exper. Med., **70**, 249, 1939. (36.) **Dubos, R. M.,** and **Hotchkiss, R. D.**: J. Exper. Med., **73**, 629, 1941. (**37.**) **Duffin, W. M.,** and **Smith, S.**: Nature, **151**, 251, 1943.

(**37***a*.) Editorial: Lancet, **2**, 236, 1940. (**38.**) Editorial: Brit. Med. J., **1**, 162, 1941. (**39.**) Editorial: Brit. Med. J., **2**, 310, 1941. (**40.**) Editorial: Lancet, **2**, 345, 1941. (**41.**) Editorial: Lancet, **2**, 189, 1942. (**42.**) Editorial: Lancet, **1**, 113, 1943. (**43.**) Editorial: New England J. Med., **228**, 295, 1943. (**44.**) Editorial: Brit. Med. J., **1**, 481, 1943. (**44***a*.) Editorial: Lancet, **2**, 106, 1943. (**44***b*.) Editorial: Lancet, **2**, 546, 1943. (**44***c*.) Editorial: Lancet, **2**, 737, 1943. (**45.**) **Emmerich, R.,** and **Low, O.**: Ztschr. f. Hyg. v. Infektionskrankh., **31**, 1, 1899. (**46.**) **Emmerich, R.,** and **Saida**: Zentralbl. f. Bakteriol., **27**, 776, 1900. (Cited by Hepler and Snow, Ref. 66.)

(**47.**) **Faxon, N. W.,** and **Churchill, E. D.**: J. Am. Med. Assn., **120**, 1385, 1942. (**48.**) **Fleming, A.**: Brit. J. Exper. Path., **10**, 226, 1929. (**49.**) **Fleming, A.**: J. Path. and Bacteriol., **35**, 831, 1932. (**50.**) **Fleming, A.**: Proc. Roy. Soc. Med., **34**, 342, 1941. (51.) **Fleming, A.**: Brit. Med. J., **1**, 547, 1942. (**52.**) **Fleming, A.**: Lancet, **1**, 732, 1942. (53.) **Fleming, A.,** and **Macleon, I. H.**: Brit. J. Exper. Path., **11**, 127, 1930. (**54.**) **Florey, H. W.,** and **Jennings, M. A.**: Brit. J. Exper. Path., **23**, 120, 1942. (**55.**) **Florey, M. E.,** and **Florey, H. W.**: Lancet, **1**, 387, 1943. (**56.**) **Foster, J. W.**: J. Biol. Chem., **144**, 285, 1942. (**56***a*.) **Foster, J. W.,** and **Woodruff, H. B.**: J. Biol. Chem., **148**, 723, 1943. (**57.**) **Foster, J. W.,** and **Woodruff, H. B.**: J. Bacteriol., **46**, 187, 1943. (**58.**) **Foster, J. W.,** and **Wilker, B. L.**: J. Bacteriol., **46**, 377, 1943. (**58***a*.) **Foster, J. W., Woodruff, H. B.,** and **McDaniel, L. E.**: J. Bacteriol., **46**, 421, 1943.

(**59.**) **Gardner, A. D.**: Nature, **146**, 837, 1940. (**60.**) **Glister, G. A.**: Nature, **148**, 470, 1941. (**61.**) **Gold, H.**: Bull. New York Acad. Med., **19**, 132, 1943.

(**62.**) **Hac, L. R.,** and **Hubert, A. C.**: Proc. Soc. Exper. Biol. and Med., **53**, 61, 1943. (**62***a*.) **Hamre, D. M., Rake, G., McKee, C. M.,** and **MacPhillamy, H. B.**: Am. J. Med. Sci., **206**, 642, 1943. (**62***b*.) **Harper, G. J. N.**: Lancet, **2**, 569, 1943. (**63.**) **Heatley, N. J.**: J. Bacteriol., **43**, 645, 1942. (**64.**) **Heilman, D. H.,** and **Herrell, W. E.**: J. Bacteriol., **43**, 12, 1942. (**65.**) **Heilman, D. H.,** and **Herrell, W. E.**: Proc. Staff Meet., Mayo Clin., **17**, 321, 1942. (**65***a*.) **Heilman, F. R.,** and **Herrell, W. E.**: Proc. Staff Meet., Mayo Clin., **18**, 457, 1943. (**66.**) **Hepler, O. E.,** and **Snow, A.**: Quart. Bull. School Med. Northwest. Univ., **17**, 218, 1943. (**67.**) **Herrell, W. E.**: Proc. Staff Meet., Mayo Clin., 18, 65, 1943. (**68.**) **Herrell, W. E., Cook, E. N.,** and **Thompson, L.**: J. Am. Med. Assn., **122**, 289, 1943. (**69.**) **Herrell, W. E., Heilman, D. H.,** and **Williams, H. L.**: Proc. Staff Meet., Mayo Clin., **17**, 609, 1942. (**70.**) **Herrell, W. E.,** and **Heilman, D. H.**: Am. J. Med. Sci., **205**, 157, 1943. (**70***a*.) **Herrell, W. E.,** and **Nichols, D. R.**: Proc. Staff Meet., Mayo Clin., **18**, 313, 1943. (**71.**) **Hobby, G. L., Meyer, K., Dawson, M. H.,** and **Chaffee, E.**: J. Bacteriol., **43**, 11, 1942. (**72.**) **Hobby, G. L., Meyer, K.,** and **Chaffee, E.**: Proc. Soc. Exper. Biol. and Med., **50**, 277, 1942. (**73.**) **Hobby, G. L., Meyer, K.,** and **Chaffee, E.**: Proc. Soc. Exper. Biol. and Med., **50**, 281, 1942. (**74.**) **Hobby, G. L., Meyer, K.,** and **Chaffee, E.**: Proc. Soc. Exper. Biol. and Med., **50**, 285, 1942. (**75.**) **Holiday, E. R.**: Brit. J. Exper. Path., **23**, 115, 1942. (**76.**) **Hoogerheide, J. C.**: Unpublished. (Cited by Foster and Woodruff, Ref. 57.) (**77.**) **Hotchkiss, R. D.,** and **Dubos, R. J.**: J. Biol. Chem., **136**, 803, 1940.

(**78.**) **Keefer, C. S., Blake, F. G., Marshall, E. K., Lockwood, J. S.,** and **Wood, W. B., Jr.**: J. Am. Med. Assn., **122**, 1217, 1943. (**79.**) **Kocholaty, W.**: J. Bacteriol., **44**, 143, 1943. (**80.**) **Kocholaty, W.**: J. Bacteriol., **44**, 467, 1942. (**81.**) **Kocholaty, W.**: Science, **97**, 186, 1943.

(**82.**) **Lewis, R. M.**: South. Med. J., **36**, 363, 1943. (**82***a*.) **Lochhead, A. G.,** and **Timonin, M.**: Canad. J. Pub. Health, **34**, 236, 1943. (**82***b*.) **Lyons, C.**: Ann. Surg., **118**, 894, 1943. (**83.**) **Lyons, C.**: J. Am. Med. Assn., **123**, 1007, 1943.

(**83***a*.) **MacLeod, C. M.**: J. Exper. Med., **72**, 217, 1940. (**84.**) **Mahoney, J. F., Ferguson, C., Buchholtz, M.,** and **Van Slyke, C. J.**: Am. J. Syph., Gonor. and Ven. Dis., **27**, 525, 1943. (**85.**) **McIntosh, J.,** and **Selbie, F. R.**: Lancet, **2**, 750, 1942. (**86.**) **McKee, C. M.,** and **Houck, G. L.**: Federation Proc., **2**, 100, 1943. (**87.**) **McKee, C. M.,** and **Houck, C. L.**: Proc. Soc. Exper. Biol. and Med., **53**, 33, 1943. (**88.**) **McKee, C. M.,** and **Rake, G.**: J. Bacteriol., **43**, 645, 1942. (**89.**) **McKee, C. M.,** and **Rake, G.**:

Proc. Soc. Exper. Biol. and Med., **51**, 275, 1942. (**90.**) **Meyer, K., Chaffee, E., Hobby, G. L., Dawson, M. H., Schwenk, E.,** and **Fleischer, G.**: Science, **96**, 20, 1942. (91.) **Meyer, K., Hobby, G. L.,** and **Chaffee, E.**: Science, **97**, 205, 1943. (**92.**) **Meyer, K., Hobby, G. L.,** and **Dawson, M. H.**: Proc. Soc. Exper. Biol. and Med., **53**, 100, 1943.

(**93.**) News Notes: Quart. Bull. Med. School Northwest. Univ., **17**, 311, 1943. (**93***a*.) **Oxford, A. E., Raistrick, H.,** and **Smith, G.**: Chemistry and Industry, **61**, 22, 1942. (Cited by Florey and Jennings, Ref. 54.)

(**94.**) **Powell, H. M.,** and **Jamieson, W. A.**: Proc. Soc. Exper. Biol. and Med., **49**, 387, 1942. (**95.**) **Powell, H. M.,** and **Jamieson, W. A.**: J. Indiana Med. Assn., **35**, 361, 1942. (**96.**) **Pulvertaft, R. J. V.**: Lancet, **2**, 341, 1943.

(**97.**) **Rammelkamp, C. H.**: Proc. Soc. Exper. Biol. and Med., **51**, 95, 1942. (**98.**) **Rammelkamp, C. H.,** and **Bradley, S. E.**: Proc. Soc. Exper. Biol. and Med., **53**, 30, 1943. (**99.**) **Rammelkamp, C. H.,** and **Helm, J. D.**: Proc. Soc. Exper. Biol. and Med., **54**, 31, 1943. (**100.**) **Rammelkamp, C. H.,** and **Helm, J. D.**: Proc. Soc. Exper. Biol. and Med. (to be published). (**101.**) **Rammelkamp, C. H.,** and **Keefer, C. S.**: Am. J. Med. Sci., **205**, 342, 1943. (**102.**) **Rammelkamp, C. H.,** and **Keefer, C. S.**: J. Clin. Invest., **22**, 425, 1943. (**102***a*.) **Rammelkamp, C. H.,** and **Keefer, C. S.**: J. Clin. Invest., **22**, 649, 1943. (**103.**) **Rammelkamp, C. H.,** and **Maxon, T.**: Proc. Soc. Exper. Biol. and Med., **51**, 386, 1942. (**104.**) **Rantz, L. A.,** and **Kirby, W. M. M.**: In press. (**104***a*.) **Raper, K. B.,** and **Coghill, R. D.**: J. Am. Med. Assn., **123**, 1135, 1943. (**105.**) **Reid, R. D.**: J. Bacteriol., **29**, 215, 1935. (**106.**) Report: Brit. Med. J., **2**, 640, 1940. (**107.**) **Richards, A. N.**: J. Am. Med. Assn., **122**, 235, 1943. (**108.**) **Roberts, E. C.,** *et al.*: J. Biol. Chem., **147**, 47, 1943. (**109.**) **Robinson, G. H.,** and **Wallace, J. E.**: Science, **98**, 329, 1943; Abstract, J. Am. Med. Assn., **123**, 840, 1943. (**110.**) **Robinson, H. J.**: J. Pharmacol. and Exper. Therap., **77**, 70, 1943. (**111.**) **Robson, J. M.,** and **Scott, G. I.**: Nature, **149**, 581, 1942. (**112.**) **Robson, J. M.,** and **Scott, G. I.**: Lancet, **1**, 100, 1943.

(**113.**) **Schmidt, L. H.,** and **Sesler, C. L.**: Proc. Soc. Exper. Biol. and Med., **52**, 353, 1943. (**114.**) **Schnitzer, R. J., Camagni, L. J.,** and **Buck, M.**: Proc. Soc. Exper. Biol. and Med., **53**, 75, 1943. (**115.**) **Siegel, H.**: Tissue Studies of Toxic Doses of Penicillin (to be published). (Cited by Robinson, H. J., Ref. 110.) (**116.**) **Spurling, G.**: Personal communication. (Cited by Lyons, Ref. 83.)

(**117.**) **Taylor, H. G.**: Proc. Soc. Exper. Biol. and Med., **52**, 299, 1943. (**118.**) **Thom, C.,** and **Church, M. B.**: The Aspergilli, Baltimore, Williams & Wilkins, p. 272, 1926. (**119.**) **Thom, C.**: The Penicillia, Baltimore, Williams & Wilkins, p. 644, 1930. (**119***a*.) **Thomson, S.,** *et al.*: Penicillin in War Wounds: A Report From the Mediterranean, Lancet, **2**, 742, 1943. (**120.**) **Tillett, W. S., Cambier, M. J.,** and **Harris, W. H.**: J. Clin. Invest., **22**, 249, 1943. (**121.**) **Turner, J. C., Heath, F. K.,** and **Magasanik, B.**: Nature, **152**, 326, 1943.

(**122.**) **Ungar, J.**: Nature, **152**, 245, 1943.

(**123.**) **Van Bruggen, J. T., Reithel, F. J., Cain, C. K., Katzman, P. A.,** and **Doisy, E. A.**: J. Biol. Chem., **148**, 365, 1943.

(**124.**) **Waksman, S. A.**: Bacteriol. Rev., **5**, 231, 1941. (**125.**) **Waksman, S. A.,** and **Woodruff, N. B.**: J. Bacteriol., **44**, 373, 1942. (**125***a*.) **Williams, H. L.,** and **Nichols, D. R.**: Proc. Staff Meet., Mayo Clin., **18**, 467, 1943. (**126.**) **Wilson, U.**: Nature, **152**, 475, 1943.

RADIOLOGY

UNDER THE CHARGE OF
HARRY M. WEBER, M.D., AND DAVID G. PUGH, M.D.
SECTION ON ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

A NEW CHOLECYSTOGRAPHIC MEDIUM

By Harry M. Weber, M.D.

Graham and Cole[7] did their original work on cholecystography using the sodium salt of tetraiodophenolphthalein. Then, finding that the sodium salt of tetrabromphenolphthalein was apparently less toxic, they used and recommended this compound for a time. Later a more refined preparation of the iodo salt was made available which was found to be not appreciably more toxic than the brom preparation, but had the inher-

ent advantage that a smaller dose of it was required to produce satisfactory cholecystograms. Since that time sodium tetraiodophenolphthalein has been the cholecystographic medium of choice the world over. However, it has never been considered the ideal preparation. In spite of many improvements in the technique of administration many patients experience disagreeable reactions such as nausea, vomiting and purging; it has not been possible to administer the compound in palatable form; occasionally, at least, the reactions have been severe enough to cast doubt on the validity of the cholecystographic findings.

Researches to discover a more satisfactory compound for cholecystographic purposes have been going on from time to time since the earliest years of cholecystography. In 1927, for instance, Kirklin and Kendall[10] had prepared the di-iodo-di-ethyl-ether of disalicylphthalein and had administered 10 gm. of the sodium salt of this compound in 100 cc. of water to patients. Their preliminary report on the use of this substance was most encouraging but the work was discontinued, presumably because the advantages that the new compound had to offer were too few over the refined preparations of tetraiodophenolphthalein and tetrabromphenolphthalein which were being made available commercially by that time. Pribram[14] in 1926 had investigated a di-iodo-atophan, called biloptin, and found that while it was not very disturbing to his patients it was shown to produce renal and hepatic damage. In 1936[15] he reported his experience with another substance, another iodized quinoline derivative, commercially called choleselectan, but for some reason this substance was not made available for any worthwhile length of time.

No other researches along these lines were reported in the roentgenologic literature in the first 15 years after the discovery of cholecystography. Since the chemical possibilities are so numerous it is probably fair to conclude that the search for a new cholecystographic drug was not very intensive after all, and this in turn might be advanced as testimony to the generally satisfactory qualities of tetraiodophenolphthalein. Its disadvantages have proved in reality to be minor ones; experienced cholecystographic interpreters have taken them into account to make the record of cholecystography with it a truly brilliant one.

In 1940 Dohrn and Diedrich,[5] of the laboratories of Schering-A.-G., Berlin, announced the synthesis of a new substance, β-(4-hydroxy-3, 5-di-iodo-phenyl)-α-phenyl-proprionic acid, the sodium salt of which was made commercially available in Germany under the name "bileselectan." It was passed out among numerous physicians over there at once and from the very beginning reports were uniformly favorable when not enthusiastic. In the last year or two the same substance has been made available in this country by the Schering Corporation under the commercial name of priodax. Apparently many roentgenologists and other physicians have given it a trial.

Einsel and Einsel,[6] for instance, reported their experience with it in 50 unselected cases. The dose was 3 gm. stirred in a cup of tea. No obnoxious symptoms were produced in any of the cases except that one patient complained of a mild burning in the "stomach." These observers concluded that a single dose of 3 gm. of priodax administered orally produced cholecystograms equal or superior to those obtained with other cholecystographic media and that freedom from nausea, vomiting and other indications of gastro-intestinal irritation was an outstanding feature of these examinations. Of further interest in this report is the observation that a good shadow of the gall bladder was obtained in 2 cases in which

previously there had not been any cholecystographic response with sodium tetraiodophenolphthalein.

Wasch[18] analyzed data on 134 cases in which priodax was used. In all but 33 of these a single dose of 3 gm. was administered suspended in water, fruit juice or milk. In the 33 cases a second dose of 3 gm. was given the following day, chiefly to check on the reliability of the original examinations. Wasch concluded that the new compound was absorbed readily by the intestine, that its administration was simple, that unfavorable reactions were negligible, that the double dose was not necessary and that in general priodax is a more desirable cholecystographic medium than sodium tetraiodophenolphthalein. He also quoted Junkmann[9] to the effect that because of the high alkalinity of solutions of the sodium salt of this new compound it is not practical to employ it intravenously.

Marshall[13] analyzed the results of the cholecystographic examination of 50 patients in which priodax was used. He gave 2 doses, each consisting of 3 gm. of the substance in tablet form, 1 after a light luncheon at noon, the other after a fat-free meal of tea and toast at 8 P.M. The tablets were swallowed whole. Marshall,[13] too, regarded these cholecystograms as very satisfactory. He concluded that priodax had advantages over sodium tetraiodophenolphthalein in that it seemed to him to be less toxic, it produced fewer disagreeable side effects, it did not act as a purgative and it seemed to be so completely absorbed in the intestine that no shadows of medium-containing intestinal loops obscured the region of the gall bladder.

These reports are encouraging. The new compound is being used quite widely now and more will be heard about it. It will be interesting to note what further experience with it will reveal. Is it actually as harmless a drug as sodium tetraiodophenolphthalein has proved to be? The phenolphthalein derivatives are excreted of course mainly *via* the intestinal tract. Junkmann[9] stated that from 61 to 83% of the new compound is excreted in the urine within 72 hours after it is taken by mouth; this is probably too slow a rate to cause appreciable harm even to previously damaged kidneys. That it is a more palatable way of taking a cholecystographic medium can hardly be questioned. The dose (3 gm.) is less than the conventional dose of tetraiodophenolphthalein (4 gm.) and a single dose seems to be adequate. Therefore, if priodax does come into more general use, it is possible that patients will no longer have to undergo the so-called double-dose technique advocated in some quarters.

If the new compound proves to be as harmless to patients as it is claimed to be, then it is possible that the cholecystographic evidence of cholecystic disease (failure of the gall bladder to accept and concentrate the media, and the manifestation of cholelithiasis) will become more reliable, if only a little. On the other hand, will the interpretation of the normal cholecystographic response have to be modified? Will more diseased gall bladders show what is now called a normal cholecystographic response with the new medium than with the old? Use of the new substance in much larger numbers of cases in which cholecystographic findings are checked carefully with pathologic and with clinical findings will supply the answers to these questions.

Some Peculiar Forms of Pneumonitis. *Pleuropulmonary Involvement in Tularemia.* Bihss and Berland[1] studied the roentgenographic findings in the lungs and pleura in 81 cases of authentic tularemia. They mentioned the 4 recognized clinical forms of tularemia, only to note that 72 of the cases were of the ulceroglandular, glandular or oculoglandular form and 9 were classified as typhoidal.

Of the group of 72 cases there were 19 in which there was roentgenologic evidence of pathologic change in the lungs, pleura or mediastinal lymph nodes. In the earlier stages of the disease there was widening of the mid-mediastinal shadow on the roentgenograms, indicating enlargement of the lymph nodes of the region. It seemed to these observers that when extension to the parenchyma of the lung or to the pleura took place, it did so in retrograde direction from the enlarged mediastinal nodes. Parenchymatous involvement was in the form of unilocular or multilocular consolidation, resembling typical or atypical bronchopneumonia; when the pleura became involved there was pleural effusion.

Seven of the 9 patients who had typhoidal tularemia had pneumonia and 2 of them gave evidence of hilar adenopathy. In these cases the parenchyma of the lung seemed to be involved primarily, usually without preceding enlargement of the mediastinal lymph nodes. The pulmonary lesions consisted of one or more massive consolidations, manifested roentgenographically by large homogeneous areas of density.

In the 53 cases of tularemia in which there was no evidence, clinical or roentgenologic, of pulmonary disease, there was but 1 death. Three of the 7 patients who had typhoidal tularemia and pneumonia died; 4 of the 19 patients who had non-typhoidal tularemia and pleuropulmonary complications died. It has been pointed out frequently that pulmonary complications of tularemia have grave prognostic implications; here is more evidence to show that such complications are not necessarily fatal.

Bihss and Berland[1] pointed out that symptoms referable to the thorax are often overlooked, especially when the local disease is severe and the patient is very toxemic. Two of their patients who had no respiratory symptoms and no physical signs of intrathoracic disease showed roentgenologic evidence of hilar adenopathy and patchy bronchopneumonia. It is possible that pneumonitis with or without involvement of the hilar lymph nodes is more common, even in the less severe cases of tularemia, than we think. When tularemia is complicated with pleuropulmonary disease the clinicoroentgenologic situation may be expected to be confusing, especially since the clinical evidence of respiratory involvement may not correlate well. Especially in regions where tularemia is relatively common, patients exhibiting pulmonary disease in any way atypical should receive the benefit of the diagnostic agglutination tests for tularemia.

Pleuropulmonary Involvement in Coccidioidomycosis. Colburn[2] studied the roentgenologic manifestations of the pulmonary lesions of 75 soldiers hospitalized during an outbreak of coccidioidomycosis which developed in association with army maneuvers in an area where the disease is endemic. The symptoms were prominently respiratory and usually developed within 14 days after exposure. All of the patients had been exposed recently to spore-laden dust, so that the incubation period was within known upper and lower limits; all showed positive coccidioidin (intradermal) reactions; positive complement fixation tests or positive precipitin tests showing titers compatible with the stage and severity of disease present were shown by all, and none gave a previous history of exposure.

In all but 3 of the cases there was definite evidence of pulmonary or pleural involvement. The lesions were of several types, depending chiefly on their anatomic distribution. In 29 cases the lesion in the lung was represented roentgenographically by a fan-shaped, mottled opacity extending from the hilus, the shadow of which was larger than was considered normal; this was interpreted as interstitial bronchopneumonia with extension of the inflammatory process to the regional lymphatic

structures. In 18 of the cases the involvement seemed to be confined to the hilar or mediastinal lymph nodes. The roentgenographic evidence for this involvement was simply an increase of the hilar density. Fairly well-circumscribed, homogeneous masses in the parenchyma of the lungs, chiefly in the lower lobes, and almost always associated with abnormal hilar shadows, were observed in 20 instances. These were considered to be lobular and sublobular exudative processes, probably essentially the same type of lesion as the interstitial bronchopneumonia described previously. Cavernous lesions were observed in 3 cases and massive pleural effusion was observed in 2.

Here, too, we are dealing with an infectious agent which often produces pulmonary lesions that resemble those produced in the more familiar forms of bronchopneumonia and lobar pneumonia so closely that the roentgenologic manifestations of all of them must of necessity be of the same kind. Coccidioidomycotic pneumonitis may be considered to be a form of atypical pneumonia. Taken by themselves the roentgenologic manifestations are not distinctive, a point which Colburn[3] emphasized. In regions where this disease is endemic, if there is any encounter with a pulmonary lesion the clinical or roentgenologic features of which are out of the ordinary, infection with *Oidium coccidiosis* must be considered among the diagnostic possibilities.

Other Forms of Atypical Pneumonia.—In recent years a hitherto relatively unfamiliar type of pneumonia either has become more prevalent or is being recognized much more frequently than before. Cases occur chiefly in large and small epidemics and sporadically as well. Many names, most of them indefinite etiologically, have been used in the descriptions of cases. The designation "virus pneumonia" came to be employed widely if somewhat loosely, chiefly because it was so often impossible to discover a pathogenic microörganism which could justifiably be considered to be the cause of the pneumonia that was present. Many observers, however, preferred to restrict the use of the term "virus pneumonia" to those cases in which one of the known viruses could be designated with certainty as the etiologic factor. They then used more or less descriptive pathologic terms, such as atypical pneumonia, acute pneumonitis, acute interstitial pneumonitis, focal pneumonia, acute diffuse bronchiolitis and many others like them, to identify the disease.

That a virus was a possible, if not the probable, etiologic agent has not been denied, but the recovery of viruses is a notoriously difficult task and the facilities for the isolation and identification of them are not accessible to many physicians, so that the exact position of the viruses as etiologic agents in the cases of atypical pneumonia is being determined rather slowly. Several viruses are known to be able to produce the clinical picture, the prominent ones among them being those of influenza A and B, psittacosis, meningopneumonitis and rickettsias. As facilities for recovering and identifying these are becoming more generally available, it appears that a virus agent is being made responsible in more and more of the instances of the type of pneumonia under discussion.

Although roentgenographic findings have been included in practically all of the reports of cases, the contribution of roentgenologists to the large literature which has accumulated on the subject of atypical pneumonia has been small, conspicuously so if consideration is given to the important part the roentgenologic examination of the lungs plays in the development of the clinical syndrome. One of the prominent features of the disease is that the symptoms and physical signs of pulmonary involvement are

disproportionately small when compared with the extent of pulmonary disease shown to be present at roentgenographic examination. It is true that one of the earliest and best descriptions of the disease as it occurs in epidemic form was made by the roentgenologist Bowen[2] in a roentgenologic journal and an excellent description of the roentgenologic manifestations in the lungs was offered by Kornblum and Reimann[11] some 5 years later.

Other than these there have been few, if any, formal considerations of this type of pneumonia in the American roentgenologic literature in the last decade; yet it is exaggerating only a little to say that this disease was discussed informally almost every time two or more roentgenologists got together in recent years. In 1943, however, there were several treatises on atypical pneumonia in the roentgenologic journals. There is so much uniformity in the reports that a review of all of the papers[4,16,17] individually seems superfluous.

McCarthy's[12] description of the pulmonary lesion as exhibited on roentgenograms seemed especially lucid. His experience was with 590 patients who were admitted to a station hospital of the United States Army and whose disease was classified as primary atypical pneumonia of unknown origin. Roentgenologic evidence of pulmonary disease appeared about the 4th day of illness.

According to roentgenologic findings the cases were divided into four groups. The largest number of cases fell into Group I. Early there was an increase in prominence of the hilar markings, usually greater on one side than on the other, and accentuation of the pulmonary markings. By the next day the evidence of pulmonary disease reached its maximum. In one or more lobes consolidation then developed which seemed to extend from the hilus. The consolidation was homogeneous and less dense than that of lobar pneumonia, since the pulmonary markings were visible through it. In Group II smaller, patchy areas of consolidation developed, usually in a single lobe. Some of these areas became confluent. The appearance resembled that of bronchopneumonia. In Group III the pulmonary change was in the form of thick strands radiating into the parenchyma of the lung from the hilus. When upper lobes were affected, the resemblance to pulmonary tuberculosis was so great that serial examinations were necessary to rule this condition out. In Group IV the pulmonary markings were increased throughout but in addition there were numerous or innumerable small areas of consolidation which brought the picture of miliary tuberculosis to mind. Patients in this group were extremely ill and the course of the disease was unusually prolonged. McCarthy[12] noted that pleural involvement was rare in the cases he observed.

Hufford and Applebaum[8] reviewed the roentgenologic and clinical findings in 27 cases which they observed in civilian practice. Only the roentgenologic aspects will be given consideration here. They emphasized that while the roentgenographic evidence of pulmonary involvement was the outstanding objective feature of their cases, the findings are not distinctive enough to enable one to make an independent roentgenologic diagnosis of atypical pneumonia. Typically their patients showed diffuse, irregular, patchy densities with feathery edges extending into the pulmonary substance from the hilus. Large areas of consolidation were not common but some coalescence often took place. In several of the cases both lungs were involved.

Comment. From a study of the articles it is apparent that the roentgenologic manifestations of atypical pneumonia are variable and not

distinctive. In some instances the roentgenologic manifestations are of such a kind that an experienced roentgenologic observer will know at a glance that he is dealing with a disease very different from the forms of lobar pneumonia and bronchopneumonia commonly encountered; in others, perhaps in the majority, such an independent distinction cannot be made. In general it may be said that pulmonary disease becomes evident roentgenographically early in the development of the disease; that the earliest evidence is an increase of the hilar shadows, often followed by a fan-shaped, poorly circumscribed area of consolidation extending from the hilus into the substance of the lung; that the consolidation is not as dense as that encountered in lobar pneumonia and that multiple lesions are fairly common, the second lesion often developing at about the time the first was beginning to undergo resolution.

It is noteworthy that none of the observers seemed able to identify the picture of "acute tracheobronchitis" which Kornblum and Reimann[11] described so beautifully. This should not reflect adversely on the validity of Kornblum and Reimann's findings nor on the observations that these authors made. Kornblum and Reimann had an unusual opportunity. The patients were all in one institution, all the roentgenologic examinations were made in similar very well-controlled circumstances and early medical attention was easily available. It is probable that the roentgenologic picture of "acute tracheobronchitis" is the earliest possible evidence of this pneumonia or in fact of any other type of pneumonia.

REFERENCES

(1.) **Bihss, F. E.**, and **Berland, H. I.**: Radiology, **41**, 431, 1943. (2.) **Bowen, A.**: Am. J. Roentgenol., **34**, 168, 1935. (3.) **Colburn, J. R.**: Am. J. Roentgenol., **51**, 1, 1944. (4.) **Curtzwiler, F. C.**, and **Moore, B. E.**: Radiology, **40**, 347, 1943. (5.) **Dohrn, M.**, and **Diedrich, P.**: Deutsch. med. Wchnschr., **66**, 1133, 1940. (6.) **Einsel, I. H.**, and **Einsel, T. H.**: Am. J. Digest. Dis., **10**, 206, 1943. (7.) **Graham, E. A.**, and **Cole, W. H.**: J. Am. Med. Assn., **82**, 613, 1924. (8.) **Hufford, C. E.**, and **Applebaum, A. A.**: Radiology, **40**, 351, 1943. (9.) **Junkmann, K.**: Klin. Wchnschr., **20**, 125, 1941. (10.) **Kirklin, B. R.**, and **Kendall, E. C.**: Radiology, **9**, 205, 1927. (11.) **Kornblum, K.**, and **Reimann, H. A.**: Am. J. Roentgenol., **44**, 333, 1940. (12.) **McCarthy, P. V.**: Radiology, **40**, 344, 1943. (13.) **Marshall, W. A.**: Am. J. Roentgenol., **50**, 680, 1943. (14.) **Pribram, B. O.**: Deutsch. med. Wchnschr., **2**, 1291, 1926. (15.) **Pribram, B. O.**: München. med. Wchnschr., **83**, 1838, 1936. (16.) **Scott, W. G.**, and **Jones, H. L., Jr.**: Am. J. Roentgenol., **50**, 444, 1943. (17.) **Seeds, A. E.**, and **Mazer, M. L.**: Am. J. Roentgenol., **49**, 30, 1943. (18.) **Wasch, M. G.**: Am. J. Roentgenol., **50**, 677, 1943.

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF MARCH 21, 1944

Intercorrelations Between Cardiovascular Variables in Healthy Men, and the Relation of Physique to These and Other Variables. JAMES M. TANNER (Hartzell Dept. of Research Therapeutics, Univ. of Penna.). In an investigation on 53 healthy students:

1. Figures for the changes in systolic and diastolic blood pressure during 20 minutes following lying down were reported.

2. The standard error of measurement of blood pressure taken by the

auscultatory technique, with certain precautions, was similar to that reported by Shock and Ogden, *i. e.*, 1.9 mm. Hg systolic and 2.84 mm. Hg diastolic.

3. Ballistocardiograms were taken 14 to 21 minutes after lying down. Aortic diameter was obtained by the Kreuzfuchs measurement. The areas under 2 complexes in each record were read. There was no significant rise or fall of mean value between the two determinations. The correlation of the two values was 0.905, with a standard error of estimation of the second from the first value of 2.48 cc., or 4.8% of the second mean value. The standard error of measurement estimated from these 2 determinations was 1.8 cc., or 3.5% of total mean value.

4. Correlations between various cardiovascular and other variables were presented. The striking thing was the lack of correlation between blood pressure and heart rate, stroke volume or cardiac output, and between cardiac output and surface area or weight. No explanation is offered at present. It is emphasized that relations between variables in a population at rest may differ entirely from relations between similar variables in a single organism under varying circumstances.

5. With the help of Dr. C. W. Dupertuis, the subjects were anthroposcopically somatotyped from photographs taken as described by W. H. Sheldon. With very small numbers of limited age range, at rest, no connection was apparent between somatotype and systolic blood pressure, heart rate, ballisto impacts, stroke volume, cardiac output, or cardiac output multiplied by mean blood pressure.

The correlation between oral temperature and endomorphy was -0.342, and between oral temperature and ectomorphy $+0.347$ ($P < 0.01$). Between respiratory rate and endomorphy it was $+0.252$ ($P = 0.039$) and between respiratory rate and ectomorphy -0.265 ($P = 0.032$). No significant correlations with mesomorphy were found.

A Rapid Method for Estimating Serum Proteins (Formula for Calculating Serum Protein Concentration). F. WILLIAM SUNDERMAN (William Pepper Laboratory of Clinical Medicine, Univ. of Penna.). When the differences in the refractive index of serum and water are plotted against the serum protein concentration, an excellent linear correlation is obtained. The statistically calculated regression line derived from this correlation may be expressed by the equation:

$$Pr = 510\ R.I._{diff.} - 1.81$$

(Pr = gm. of protein per 100 ml.; R. $I._{diff.}$ = the refractive index of serum minus the refractive index of water.) The standard deviation for this regression line is equal to 0.31 gm. per 100 ml.

The method for estimating serum protein from refractivity measurements is economical in time, easy of manipulation, requires no reagents, and is useful in guiding therapy in cases of shock.

Topical Projection of the Cochlea to the Cerebral Cortex of the Monkey. CLINTON N. WOOLSEY and EDWARD M. WALZL (Department of Physiology and the Otological Research Laboratory, School of Medicine, Johns Hopkins Univ., Baltimore, Md.). The type of study previously described for

the cat (Woolsey and Walzl, *Bull. Johns Hopkins Hosp.*, **71**, 315, 1942) has been extended to the monkey. Single condenser discharges were delivered through fine wire electrodes to nerve fibers at the dissected edge of the osseous spiral lamina. Amplified contralateral or ipsilateral cortical electrical responses were visualized oscillographically and photographed. The inferior and the superior banks of the Sylvian fissure were explored. In addition the auditory area was defined by click stimulation of the intact ear.

Both methods revealed that the auditory area occupies most of the inferior Sylvian bank from its caudal end to a level 4 to 6 mm. rostral to the caudal limit of the insula. Usually the area extends everywhere to within 1 mm. of the lip of the Sylvian fissure, while caudally it may spread over the lateral surface of the temporal lobe as far as the superior temporal sulcus. The area traverses the bottom of the posterior Sylvian fissure and extends for about 3 mm. onto the superior Sylvian bank posterior to the insula. The apex of the cochlea projects to the most rostral part, the middle turn to the region lateral to the posterior end of the insula and the basal coil to the remainder of the area. The cortical area for the most basal end apparently traverses the bottom of the posterior Sylvian fissure to occupy a part of the superior bank.

In the cat a "second" auditory area, organized in a pattern inverse to that of the "primary" auditory area, was found. The presence of a similar "second" auditory system in the monkey has not yet been proved; but the evidence indicates that it exists deep within the Sylvian fissure on the lateral wall of the inferior limiting sulcus of the insula and on the dorsal bank of the posterior Sylvian fissure.

Certain homologies of the cerebral hemispheres of cat and monkey have been clarified by comparing data secured in studies of auditory, visual and somatic sensory systems of these animals.

The Metabolism of Tryptophane by Staphylococcus Aureus as a Critical Factor in Relation to the Mode of Action of Sulfonamides. By M. G. SEVAG and M. N. GREEN (Department of Bacteriology, School of Medicine, Univ. of Penna.). Our studies show that the metabolism of tryptophane by resistant and susceptible strains of *S. aureus* is a keystone to understanding of the mode of action of sulfonamides. Three aspects of tryptophane metabolism have been studied: (*a*) tryptophane as an essential amino acid; (*b*) tryptophane as the precursor of one or several arylamines (p-aminobenzoic acid?) produced during the growth of staphylococci; and (*c*) sulfonamide-antagonist action of tryptophane.

Staphylococci must either synthesize tryptophane from other amino acids or tryptophane must be provided within the medium. Arylamine is not formed when both tryptophane and glucose are omitted from the medium. Growth takes place with or without the formation of arylamine. Largest amounts are formed under conditions least favorable for growth. Even the largest amounts of arylamine produced do not exercise antisulfonamide action. These facts refute the postulates by Landy *et al.* that staphylococcal resistance to sulfonamides depends upon the synthesis of larger amounts of para-aminobenzoic acid. There is as yet no chemical evidence that staphylococci synthesize or require para-aminobenzoic acid.

In the presence of glucose and amino acids (tryptophane absent), with

or without pantothenic acid and riboflavin, the growth of staphylococci is inhibited by sulfonamides. The addition of tryptophane to the medium abolishes this inhibition by 50% in the absence of, and completely in the presence of pantothenate and riboflavin. These facts show that *sulfonamides inhibit the oxidative-reductive reactions leading to the synthesis of tryptophane, and are incapable of inhibiting the utilization of tryptophane added to the medium.* Pantothenic acid and riboflavin are participants in some manner in the metabolism of glucose and tryptophane. This is in extension of the previously formulated "inhibition of oxidative enzymes theory." (Sevag, M. G., and Shelburne, M., *J. Bacteriol.*, **43**, 411, 421, 447, 1942; Sevag, M. G., Shelburne, M., and Mudd, S., *J. Gen. Physiol.*, **25**, 805, 1942; Sevag, M. G., Henry, J., and Richardson, R., AM. J. MED. SCI., **205**, 877–878, 1943.)

BOOK REVIEWS AND NOTICES

PSYCHOSOMATIC DIAGNOSIS. By FLANDERS DUNBAR, M.D., MED.SC.D., PH.D., Department of Medicine and Psychiatry, Columbia University. Foreword by LEONARD G. ROWNTREE, Colonel, Medical Reserve Corps, U. S. Army. Pp. 741; 15 charts, 12 tables. New York, London: Paul B. Hoeber, Inc., 1943. Price, $7.50.

THE appearance of this new volume marks another milestone in the advance of psychosomatic medicine. The concepts of this school have been widely disseminated in recent years by the journal, *Psychosomatic Medicine*, by Weiss and English's recent text-book, and by very numerous original articles. Those in touch with the medical problems of the present war, which are characterized by a high incidence of functional disorders, are finding the contribution of the psychosomatic school to be a valuable aid in the better understanding and handling of such cases.

"Psychosomatic Diagnosis" is a voluminous report on the study made by Dr. Dunbar and her associates on 1600 patients admitted to the wards of a general hospital, suffering from the following illnesses: rheumatic and cardiovascular disease, diabetes, and fracture. The admission diagnosis in each case was an organic one; Dr. Dunbar and her assistants interviewed each of these patients in order to discover the psychic component, and especially to see whether a characteristic personality pattern or socio-familial background was specific for each of the diseases studied. Such proved to be the case, and not the least surprising finding was that of a specific predisposition to accident-habit in the majority of patients on the fracture wards, which unexpectedly prevented the contemplated use of this group as normal controls. Careful personality "profiles" are presented for each group, but an indication of the personality types is also given by the semi-facetious labels suggested by the author: "Hobo" for the fracture patients, "would-be top-dogs" for the hypertensives, "teachers' pets" and "martyrs" for those with rheumatic fever or rheumatic heart disease, and "muddlers" for the diabetics.

A chapter on how to take an informative psychosomatic history adds to the practical value of this scholarly report. D. P.

THE MODERN MANAGEMENT OF COLITIS. By J. ARNOLD BARGEN, M.D., M.S., F.A.C.P., Chief of the Section on Internal Diseases, Division of Medicine, Mayo Clinic; Associate Professor of Medicine, Mayo Foundation, Rochester, Minn.; Secretary, American Gastroenterological Association; Vice-Chairman, Section on Gastroenterology and Proctology, American Medical Association. Pp. 332; 148 figs. Springfield: Charles C Thomas, 1943. Price, $7.00.

DR. BARGEN is indeed qualified to write a monograph on the colon because of his rich clinical and experimental experience at the Mayo Clinic. The book is timely because of the prevalence of intestinal disorders in time of war and turmoil.

Anatomy and physiology of the colon, as well as methods of study of patients with colon complaints, are thoroughly discussed. There is a chapter on the "irritable colon" (mucous colitis) which presents the latest concepts concerning the etiology and treatment of this common functional disease.

The organic types of colitis are divided into 9 groups: (1) Thrombo-ulcerative (streptococcal). (2) Regional (segmental) ulcerative. (3) Chronic ulcera-

tive. (4) Tuberculous ulcerative. (5) Amebic ulcerative. (6) Food and vitamin deficiency type. (7) Lymphogranulomatous ulcerative. (8) Allergic. (9) Chronic ulcerative following bacillary dysentery. In each of these groups etiology, pathologic lesions, symptoms, diagnostic criteria, treatment, and complications are thoroughly discussed.

An entire chapter is devoted to conditions to be distinguished from colitis. Diseases to be considered are: polyposis, carcinoma, regional enteritis, diverticulosis and diverticulitis, food poisoning, parasitic dysentery, nonspecific granuloma, actinomycosis, appendicitis, Meckel's diverticulitis, sprue, pellagra, pernicious anemia, exophthalmic goiter, uremia, fecal impaction, foreign bodies, volvulus and intussusception, failure of rotation of the colon, benign stricture, anal infection, hemorrhoids, agranulocytic angina, diseases of gall bladder, and urinary tract diseases.

In conclusion the author stresses that the symptoms of colitis may be a reflection of many bodily disorders extrinsic to the bowel. L. LaT.

PATHOLOGY AND THERAPY OF RHEUMATIC FEVER. By LEOPOLD LICHTWITZ, M.D., Lately, Chief of the Medical Division of the Montefiore Hospital, and Clinical Professor of Medicine, Columbia University, New York City. Foreword by WILLIAM J. MALONEY, M.D., LL.D., F.R.S. (EDIN.), Consulting Neurologist to the City Hospital; Formerly Professor of Nervous and Mental Disease, Fordham University, New York City. Edited by MAJOR WILLIAM CHESTER, M.C. Pp. 211; 60 figs. New York: Grune & Stratton, Inc., 1944. Price, $4.75.

THIS is a very dangerous book. It is written in the authoritarian manner, characteristic of continental writers, which unfortunately is often accepted at its assumed value by the careless reader. In this instance this acceptance might the more readily happen, since in the Foreword the author is named "our foremost authority on the pathology of function.!"

An author, of course, has a right to state his opinions but only as opinions, not as facts. In this instance the author accepts the view that rheumatic fever is caused by sensitization to antigens, but he widens the list of offending antigens to include both non-pathogenic organisms and foreign proteins "not of microbic origin." The rôle of the streptococcus is not stressed—in fact it is scarcely touched on; nor does the word "streptococcus" appear in the index. This leads to some absurdities such as the inclusion of epidemic pleurodynia as a rheumatic manifestation in the nervous system, and attributing this disease to previous vaccination or some other active immunization. Also, the flat acceptance of overgrowth of fingers and big toes as a result of "chronic" rheumatic fever is a good example of the uncritical fashion in which material is included.

It is the hope of the Reviewer that these comments will lead the reader of the book to use his critical judgment throughout. P. P.

MEDICAL PARASITOLOGY AND ZOÖLOGY. By RALPH WELTY NAUSS, B.Sc., M.D., DR.P.H., Assistant Professor of Public Health and Preventive Medicine, Cornell University Medical College; Consulting Parasitologist, New York Hospital; Fellow, American Public Health Association; Lieutenant-Colonel and Flight Surgeon, Medical Reserve Corps, U. S. Army. Foreword by JOHN C. TORREY, PH.D., Professor (Emeritus) of Epidemiology, Cornell University Medical College. Pp. 534; 95 figs. New York, London: Paul B. Hoeber, Inc., 1944. Price, $6.00.

THIS book is said to be an attempt to present essentials in brief form and so to replace larger and more complete texts now available. Less extensive it is, but claims to conciseness cannot be allowed. For example, what is a non-migrating *Endamœba coli* (p. 13) and why is this "a comparatively innocu-

ous species" (p. 17)? It is non-pathogenic without equivocation. The statement "The cyst is usually the only form in which *E. histolytica* remains viable after passing the normal acid stomach" implies rather gross fecal contamination of food, and by comparatively fresh feces at that (p. 26). Interpretations of the development of amebiasis in man (pp. 28 and 29) draw unwarranted assumptions from experimental infections in cats; and in this section the statement that experiments by Nauss and Rappaport (1940) are "substantiated" by reports published 2 years earlier is, at least, novel. The resurrection of Kofoid's report (1922) of *E. histolytica* in Hodgkin's disease (p. 37) seems unfortunate. The section on infection by intestinal protozoa lacks any statement of incidence in spite of abundant records. Further, there is no indication of the significance of *Trichomonas vaginalis* infection, and the admonition that transfers of this organism to mouth and rectum be prevented is a bit excessive in view of recent experiments. On page 59, organisms of the genus *Leishmania* are said to be transmitted through feces of insects when those which occur in man are certainly not. "Endothelium" is substituted for macrophage cells (p. 62), "leukemia" is given as a symptom of kala-azar instead of leukopenia (p. 65), and animal inoculation is suggested as an aid to diagnosis of this disease when it is well known that few animals are susceptible and incubation is prolonged. Occurrence of *Leishmania donovani* in oral and nasal secretions is not mentioned, yet this seems to be an important factor in spread of infection. On page 90 "merocyte" is used for merozoite. In several parts of the section on malaria sporozoites are said to invade erythrocytes when all evidence is against this. The exoerythrocytic phase of Plasmodium becomes "extra erythrocytic" (p. 113). Also to be questioned is the statement that *Ascaris lumbricoides* "sometimes (becomes) attached to the mucosa, which they are probably able to pinch off in small masses" (p. 147), and there is no clear statement of how hookworms cause anemia.

These are not isolated instances; many others could be cited. They illustrate rather marked incoherence, carelessness and poor organization. Everything contained in the book is presented in better form elsewhere, and the glossary is no substitute for a dictionary. H. R.

PIONEERS OF PEDIATRICS. By ABRAHAM LEVINSON, M.D., B.S., Assistant Professor of Pediatrics, Northwestern University Medical School; Professor of Pediatrics, Cook County Graduate School of Medicine; Attending Pediatrician, Children's Division of the Cook County Hospital; Senior Attending Pediatrician, Sarah Morris Hospital for Children of the Michael Reese Hospital; Senior Attending Pediatrician, Mount Sinai Hospital, Chicago. Second ed., revised and reset. Foreword by ISAAC A. ABT. 15th Publication in *Historia Medicinæ* series. Pp. 119; many pictures. New York: Froben Press, 1943. Price, $2.00.

THIS second edition, appearing 7 years after the first, is the 18th Publication in the *Historia Medicinæ* series of the Froben Press. Professedly "a bird's eye view of pediatric progress as reflected in the contributions of pioneers in the field," this compendium should be evaluated on the basis of wisdom of selection, accuracy and readability, rather than for completeness and reference value. One comes regretfully to the conclusion that at least two of the three qualities sought for have not been attached. Perhaps the attempt to cover too much ground has been the cause of a dry condensed style that, for the most part, is even less entertaining than the average catalogue raisonne. As to selection, while personal comparisons, which are especially apt to be odious and fruitless, will not be made here, the Reviewer must express a general opinion that there are many errors of both omission and commission in the "pioneers" selected. However, while most readers will prefer to go to Ruhräh's excellent source book, "Pediatrics of the Past," for their historical personages in pediatrics, this more recent production also has its field. Finally, the list of American contributions and the 4½ page bibliography are useful but do not compensate for the lack of an index. E. K.

THE MARCH OF MEDICINE. New York Academy of Medicine Lectures to the Laity, 1943. Pp. 151; no illus. New York: Columbia University Press, 1943. Price, $2.00.

THIS 8th Series of the Academy's Lectures to the Laity demonstrates how widely the scope of the series has been enlarged since their beginning. No longer merely descriptive of this or that disease or group of diseases, they treat, this year, for instance, of such topics as Crime and Punishment (Bernard Glueck); The Scientific Method and Our Plans for Peace (Sir Norman Angell); War and Medicine (Edgar Erskine Hume); Aggressiveness—Individual and Collective (Franz Alexander); Let Babies Be Our Teachers (Myrtle McGraw); and Nature and Man, The Linsly R. Williams Memorial Lecture (Robert R. Williams). Thus, psychiatric problems—human behavior—and the relation of medicine and science to society and the world crisis appropriately dominate the series, though not to the exclusion of more directly scientific subjects such as enzymes and historical medicine, for instance. To those already acquainted, the series needs no endorsement; those yet unacquainted can be assured that an evening's reading will not go unrewarded. E. K.

ESSENTIALS OF DERMATOLOGY. By NORMAN TOBIAS, M.D., Senior Instructor in Dermatology, St. Louis University; Assistant Dermatologist, Firmin Desloge and St. Mary's Hospitals; Visiting Dermatologist, St. Louis City Sanitarium and Isolation Hospital; Fellow, American Academy of Dermatology and Syphilology; Diplomate, American Board of Dermatology and Syphilology. Second ed. Pp. 497; 143 figs. Philadelphia, London, Montreal: J. B. Lippincott Company. Price, $4.75.

THE present Reviewer had the pleasure of reviewing the first edition of this now popular work (AM. J. MED. SCI., **202**, 276, 1941) and recommending it "for the student and general practitioner who does not have the facilities nor the inclination to consult a larger volume." In the second edition most of the criticisms leveled against the first edition have been scrupulously heeded. Many portions have been rewritten or considerably elaborated for the sake of clarity. Close attention has been paid to certain live subjects, such as vitamin and sulfonamide therapy and the new ointment bases. Nineteen additional photographs have been included in the revision. A new feature of this edition, not mentioned in the Preface, is the utilization of the inside of the covers and the fly-leaves for a compilation on the sulfonamide drugs in dermatology and a listing of the normal values of various blood constituents and of various tests. The Reviewer again recommends this compend as one of the best of the shorter works on dermatology. H. B.

HEALTH AND HYGIENE. A Comprehensive Study of Disease Prevention and Health Promotion. By LLOYD ACKERMAN, Western Reserve University. Pp. 895; 59 figs; 27 tables. Lancaster, Pa.: The Jacques Cattell Press, 1943. Price, $5.00.

THIS book attempts to cover the main problems of hygiene in terms which should be understandable by the general public. The author has succeeded remarkably well in meeting this difficult assignment and has produced a book of considerable merit. He believes that comprehensive courses in hygiene should be given to college students in their junior and senior years, and the book should have great value for such a purpose. It also should prove very useful to educated members of the general public and enable them to understand the elements of prevention of infection, vaccination, and the development of immunity, as well as nutrition and social health. Considerable attention is given to the evolution of health concepts with an account of the development of medicine from the early days of Æsculapius through Paracelsus to the present day. The position of special cults such as allopathy, homeopathy,

osteopathy, chiropractic and Christian Science in this development is indicated. There are interesting commentaries on the common factors in homeopathic, Christian Science and Æsculapian practices. The author quotes original sources, and references may be found in this book to "Christian" religious literature from Genesis to Mrs. Eddy. With this evidence the reader should be able to form opinions on the virtues and weaknesses of various cults.

Throughout the book the author has attempted to present the main pertinent facts, while allowing the reader to draw his own conclusions. Sometimes he might be accused of giving a biased presentation of the data, but for the most part, the facts are simply stated so that logical deduction seems obvious.

The sections on mental health, reproduction and drug action (including the effects of alcohol and nicotine) are written in a frank and interesting manner. On such controversial matters, however, the author is bound to find disagreement among his readers, though this Reviewer would quarrel with little of it. No sane reader should be offended by the unbiased presentation of the basic facts. For student use, the inclusion of a large section on psychology seems questionable to this Reviewer. It is not always advisable to encourage introspection in either early or late adolescence, though if introspection has already started, these sections should prove useful.

The various chapters include lists of literature which should enable a student to sample original sources and to follow the present trends of development. Useful tables are given of the nutritional values and compositions of various foodstuffs, as well as data on their vitamin content. While the book covers a wide field from vital statistics through nutrition to psychology, the views presented appear to be up-to-date and to be well supported by references to recent literature. H. B.

BIOLOGICAL SYMPOSIA. Edited by JACQUES CATTELL, Editor of "The American Naturalist" and "American Men of Science." Volume X. Frontiers in Cytochemistry. The Physical and Chemical Organization of the Cytoplasm. Edited by NORMAND L. HOERR, Professor of Anatomy, School of Medicine, Western Reserve University. Pp. 334; 105 figs. Lancaster, Pa.: The Jacques Cattell Press, 1943. Price, $3.50.

THIS tenth volume of Biological Symposia is presented as a tribute to Professor R. R. Bensley, Professor Emeritus of Anatomy of the University of Chicago, and includes 15 papers covering much of our present knowledge of cellular structure. The contributions include discussion of the chemistry of cytoplasm (electrolytes, nucleic acids, nucleoproteins, minerals), the morphology of cytoplasm (cytoplasmic components, ultrastructure, macromolecular particles), the respiration of cells (biologic oxidation-reduction reaction systems), and the pathology of certain types of cells (cancer cells and degenerating motoneurones). The material in this book represents the groundwork upon which important new medical discoveries may well be based. It should be a valuable addition to the libraries of those who are actively seeking further understanding of cellular functions. The printing and illustration of this volume follows the high standard set in previous editions of Biological Symposia. J. C.

PRIMER CONGRESO NACIONAL SOBRE ENFERMEDADES ENDEMO-EPIDEMICAS. First National Congress on Endemo-epidemic Diseases, held at the "Instituto Jose Penna," School of Medical Sciences of Buenos Aires, November, 1942. Pp. 679; many tables and figs. Buenos Aires: Revista Oral de Ciencias Medicas, 1943.

THE articles reported in this volume were presented at the First National Congress on Endemo-epidemic Diseases held at the "Instituto Jose Penna" under the auspices of the School of Medical Sciences of Buenos Aires. The Congress consisted of eight sessions, devoted to problems of diphtheria;

exanthematic typhus and other diseases recently found in this part of the continent; brucellosis and poliomyelitis; and diseases of the respiratory tract. The last three sessions were allocated to all other diseases. The sessions on diphtheria included articles on the different clinical manifestations, prophylaxis, treatment, epidemiology; as well as bacteriologic studies which comprised immunity, pathogenicity, allergy, relationship between clinical form of the disease to the bacterial type of the diphtheria bacillus, and so forth. In the meeting on exanthematic typhus papers were also read on yaws, "fievre boutonneuse," and "mal de pinto;" at the meeting on brucellosis papers on hidatidosis and Chagas' diseases, a social problem in South America, were also included. The diseases of the respiratory tract considered were the pneumonias and influenza. Problems of prophylaxis, immunity, diagnosis, treatment and epidemiology were discussed. In the final sessions papers on bacillary dysentery, salmonellosis, typhoid, malaria, measles, tuberculosis, leprosy, anthrax, bubonic plague and trichinosis were read.

The book is a valuable aid in comprehending the work that is being done in Argentina and the progress toward the solution of the problems involved. Most of the articles do not contain a bibliography, an omission that limits the usefulness of the book for those seeking further information. Some scientists from Uruguay collaborated in the Congress, and, consequently, their papers are included in the volume. L. G.

QUANTITATIVE PHARMACEUTICAL CHEMISTRY. By GLENN L. JENKINS, PH.D., Professor of Pharmaceutical Chemistry, College of Pharmacy, University of Minnesota, and ANDREW G. DU MEZ, PH.D., Professor of Pharmacy and Dean of the School of Pharmacy, University of Maryland. Second ed., 6th impression. Pp. 466; 67 figs. New York and London: McGraw-Hill Book Company, Inc., 1937.

THIS is a well-written book for students of pharmacy, and outlines clearly the methods used in official pharmaceutical analyses. It is to be regretted, however, that this pharmacy text does not concern itself more with the newer pharmacologic agents and less with the older, infrequently used drugs. A new edition including the changes incorporated in the *U. S. Pharmacopœia XII* and *National Formulary VII* could correct this failing. J. C.

ORAL PATHOLOGY. A Histological, Roentgenological, and Clinical Study of the Diseases of the Teeth, Jaws, and Mouth. By KURT H. THOMA, D.M.D., Professor of Oral Surgery and Bracket Professor of Oral Pathology, Harvard University; Oral Surgeon and Chief of Dental Service, Massachusetts General Hospital; Oral Surgeon to Brooks Hospital; Dental Surgeon to Dental Department and Consultant in Oral Surgery to Tumor Department, Boston Dispensary and Joseph H. Pratt Diagnostic Clinic; Consulting Oral Surgeon, New England Baptist Hospital; Consulting Oral Surgeon, Beth Israel Hospital. Second ed. Pp. 1328; 1388 figs. (128 in color); 49 tables. St. Louis: C. V. Mosby Co., 1944. Price, $15.00.

WE are glad to see the second edition of this valuable work, but suggest a more precise title for future editions. To quote from the Preface to this edition, the sentiment of which we endorse—"The surprisingly great demand which rapidly depleted the first edition of *Oral Pathology* has made it necessary to bring out this second edition. The interest which the profession has taken in this book, the content of which is almost purely scientific, is an auspicious indication of the trend in dentistry. Not only the student, but also the man who has been in practice for years, feels the need for the scientific background which the study of pathology alone can give. Thus dentistry has recognized the value of basic knowledge as a foundation for its clinical development. The ability to diagnose and treat disease intelligently is based on a thorough understanding of both disease processes and their

many and varied causes. . . . . additions have been made to include a few of the rarer diseases that are omitted from the first edition and to bring the book up to date. A number of new illustrations have been added and others have been replaced." We note too many errors, even though perhaps typographical (such as on p. 848, lii; p. 1270, l, 14.) E. K.

BIOMICROSCOPY OF THE EYE. Slit Lamp Microscopy of the Living Eye, Vol. I. By M. L. BERLINER, M.D., Assistant Professor of Clinical Surgery (Ophthalmology), Cornell University Medical College; Associate Attending Surgeon, New York Hospital; Assistant Surgeon, New York Eye and Ear Infirmary; Instructor in Biomicroscopy, Post-Graduate School, New York Eye and Ear Infirmary; Senior Associate Attending Ophthalmologist, Beth Israel Hospital, New York. Pp. 709; 512 illus. (40 pages color plates). New York, London: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1943. Price, $17.50.

THIS is the first appearance in America of an original volume on slit-lamp microscopy of the human eye. The chapters include a history of the developments of biomicroscopy, the technique of biomicroscopy and the normal findings in the anterior segments of the globe exclusive of the iris, vitreous and lens. Developmental anomalies, inflammatory lesions, traumatic injuries and degenerations, and dystrophies are then considered in the various chapters. The text is excellent and the illustrations are by far the best that have appeared from an American press. The book is undoubtedly on a par with that of Vogt, and it will be warmly welcomed by all American ophthalmologists.

F. A.

BACKACHE AND SCIATIC NEURITIS. By PHILIP LEWIN, M.D., F.A.C.S., Associate Professor of Bone and Joint Surgery, Northwestern Univ. Medical School; Attending Orthopedic Surgeon, Cook County Hospital; Attending Orthopedic Surgeon, Michael Reese Hospital; Professor, Orthopedic Surgery, Cook County Graduate School of Medicine, Chicago; Lieutenant Colonel, Medical Corps, U. S. Army. Pp. 745; 235 figs. Philadelphia: Lea & Febiger, 1943. Price, $10.00.

THIS is a very difficult book to review, for Dr. Lewin has attempted to compress an amazing amount of information in his book. His charts and diagrams at the beginning of many of the chapters show originality and disclose a method that could be well utilized in the teaching of students. These are very ingenious and informative.

In the cuts the author is remarkably clear; they deserve high praise. The Roentgen rays, photographs and line drawings and anatomic pictures are consistently good and show a tremendous amount of work and meticulous care in assembling.

The book can be recommended as being up to the minute in the great diversity of conditions that are considered in the very difficult subject of backache and sciatic neuritis. P. C.

ON THE INFLUENCE OF TRADES, PROFESSIONS, AND OCCUPATIONS IN THE UNITED STATES, IN THE PRODUCTION OF DISEASE. (Reprinted from *Transactions of the Medical Society of the State of New York*, 3, 91, 1837.) By BENJAMIN W. MCCREADY, M.D. Introductory Essay by GENEVIEVE MILLER, M.A. (Publications of the Institute of the History of Medicine, The Johns Hopkins University. Fourth series: Bibliotheca Medica Americana, vol. 4). Pp. 127. Baltimore: The Johns Hopkins Press. Price, $1.75.

AFTER a series silence of several years, the Johns Hopkins Institute of the History of Medicine now publishes a fourth volume of the Bibliotheca Medica Americana.

The McCready text of a century ago is much less important than Thacher's,

John Morgan's and Wm. H. Welch's that constitute the first 3 of the series (see AM. J. MED. SCI. Review, **195**, 370, 1938). It is also much less well known; so that, if it is as meritorious as Miss Miller's Introduction indicates, a reprint is a useful addition to American medical historical sources.

Written as a prize competition essay when the author, aged 23, was but 2 years out of medical school, the successful essay was published in an obscure journal with a circulation of but 100 copies. It is unlikely, in Miss Miller's phrase, that it "ever attracted any attention or had any influence." This first treatise on occupational diseases written in this country, then, is chiefly valuable as a good picture of the subject 100 years ago for the use of future medical historians. The author went on to the life of a busy practitioner and medical teacher in New York City. He died in 1892 without contributing further to the subject of his essay. E. K.

A SYNOPSIS OF SURGICAL ANATOMY. By ALEXANDER LEE MCGREGOR, M.CH. (EDIN.), F.R.C.S. (ENG.), Lecturer on Surgical Anatomy, Univ. of Witwatersrand; Assistant Surgeon, Johannesburg General Hospital. Fifth ed. Foreword by SIR HAROLD J. STILES, K.B.E., F.R.C.S. (EDIN.). Pp. 710; 696 illus. Baltimore: Williams & Wilkins, 1943. Price, $6.50.

THE fact that this small volume is now in its 5th edition is mute testimony to its wide popularity. The emphasis on the practical and functional aspects of anatomy makes it especially useful as a quick reference in clinic or operating theater. The first half deals with the anatomy of the normal, the last half with the abnormal. (The semi-diagrammatic line drawings with which the volume is profusely illustrated serve to aid in fulfilling these objectives.) In the latter section of the book the Author brings out the signs through which evidence of anatomic abnormality may be elicited.

The value of the work is further enhanced by the inclusion of many bibliographic references to special articles—and this new edition serves to bring these references up to date. Outline form, with economy of words, is employed throughout. As a supplement to standard works on anatomy, this book will be found very useful by students and practitioners of surgery. J. L.

CLINICAL TROPICAL MEDICINE. By Twenty-seven Authors. Edited by Z. TAYLOR BERCOVITZ, M.D., PH.D., F.A.C.P., Assistant Clinical Professor, New York Post-Graduate Medical School, Columbia Univ.; Physician in Charge, Parasitology Service, Department of Health, City of New York; Consultant in Tropical Medicine, Ellis Island Hospital, U. S. Public Health Service. Foreword by WILBUR A. SAWYER, M.D., Director, International Health Division, Rockefeller Foundation. Pp. 957; 121 figs; 11 tables. New York, London: Paul B. Hoeber, 1944. Price, $14.00.

IN keeping with the present trend toward edited works, this most recent American book on tropical diseases has 27 contributors, all well qualified. The bulk of the material, however, was prepared by the Editor, Z. T. Bercovitz, C. F. Craig, Henry Pinkerton, Howard Fox, E. Vedder and Morris Moore. Except for the first section, which deals with the diarrheal diseases and includes amebic as well as bacillary dysentery and cholera, the subject matter is arranged according to etiologic agents. This in itself will be a great aid to the novice. The sections include: diseases caused by blood protozoa, by spirochetes and spirilla, by rickettsia; viral diseases, bacterial infections and nutritional disturbances. Also included are sections dealing with diseases caused by yeasts and fungi, infestation by helminths, tropical snakes and poisonous insects, and a concluding section on the effects of heat, hygiene and sanitation.

The individual diseases are considered under the following headings: historical note, etiology, epidemiology, pathology, symptomatology, complications, laboratory and differential diagnosis, treatment and prophylaxis. Of

particular interest is the detailed discussion of laboratory procedures which often, *e. g.*, in amebic dysentery and protozoan diseases of the blood, can be carried out by the physician himself. An excellent series of 10 plates on the intestinal protozoa, as well as plates devoted to the malaria parasites and eggs of the helminths will prove useful. The clinical photographs are on the whole quite good. Though several microphotographs of tissue lesions are included, their number might well be greater. This because most men who will use the book never had formal instruction in the pathology of these diseases and hence will find it difficult to form a mental picture from the written description.

The discussions on therapy are brief, yet adequate. One is struck by the number of specific drugs which are available for treating these diseases. However, realizing that they are parasitic rather than degenerative in character this should not occasion undue surprise in our era of chemotherapy. The volume is well bound and printed; the paper is of good quality. This book should prove of value not only to physicians in the armed forces, but to the general practitioner as well. H. S.

THE CHEMISTRY OF ORGANIC MEDICINAL PRODUCTS. By GLEN L. JENKINS, Dean and Professor of Pharmaceutical Chemistry, School of Pharmacy, Purdue University; and WALTER H. HARTUNG, Professor of Pharmaceutical Chemistry, School of Pharmacy, The Univ. of Maryland. Second ed. Pp. 675; 71 tables; many small figs. New York: John Wiley & Sons, 1943. Price, $6.50.

THE organic compounds of the *materia medica* have been classified into groups according to chemical function, some 14 classifications being discussed. Thus their chemistry, their preparation and properties can be correlated effectively. The therapeutic uses are indicated in many instances, and some idea is given of the relative importance of the various compounds.

The text is an excellent presentation of the rôle of organic chemistry in the formulation and development of medicinal products. It should be of particular value to students and workers in fields related to medical science.

This 2d edition has been greatly improved by a complete revision. Some chapters have been rewritten, and a new chapter discussing "Some Physicochemical Properties of Medicinal Products" has been included. It is quite up to date. H. V.

THE PERMEABILITY OF NATURAL MEMBRANES. By HUGH DAVSON, D.Sc., Associate Professor of Physiology at Dalhousie Univ., Canada; formerly Demonstrator in Biophysics and Beit Memorial Fellow, University Coll., London, and JAMES FREDERIC DANIELLI, D.Sc., A.I.C., Bein Memorial Research Fellow and Fellow of St. John's Coll., Cambridge, England. Foreword by E. NEWTON HARVEY, Professor of Physiology in Princeton Univ. Pp. 361; 73 figs.; 72 tables. Cambridge: University Press; New York: Macmillan, 1943. Price, $4.75.

THIS timely book brings together the significant material that has resulted from studies upon permeability of many writers during the last 20 years. The book is comprised of 21 chapters and an Appendix. The first chapter deals with the significance of permeability studies and the second with methods of studying membrane permeability including chemical electrical, and radioactive isotope methods. Chapter 3 presents a discussion of equilibrium conditions of cells, and Chapter 4, the more important equations used in permeability studies. In later chapters the process of diffusion, the structure of the plasma membrane, and the interpretation of permeability measurements are considered. Permeability to non-electrolytes, gases, water, proteins and lipoids, ions and weak electrolytes and dyes are covered in the succeeding chapters. Impedance, potential measurements, the effect of narcotic substances and temperature are followed by chapters on hemolysis and the membrane permeability to secretion. A chapter is devoted to the function of

the kidney, and the final chapter, to theories of cell permeability. An Appendix on the theory of penetration of a thin membrane completes the book.

The advance in our knowledge of permeability has depended largely upon the contributions of surface chemistry and the physico-chemical structure of liquids and solids. In this book, written by two men who have contributed a great deal to our knowledge of the subject, the relevant and significant material has been carefully selected from the mass of data upon the subject. In addition, a valuable bibliography follows each chapter.

Everyone interested in biologic processes should certainly have this book at hand. When it is coupled with Bourne's recent "Cytology and Cell Physiology," a comprehensive survey of our modern concepts of the cell and its functions is obtainable. D. C.

AN OUTLINE OF GENERAL PHYSIOLOGY. By L. V. HEILBRUNN, PH.D., Professor of Zoölogy, Univ. of Penna. Second ed., revised. Pp. 748; 135 illus. Philadelphia and London: W. B. Saunders, 1943. Price, $6.00.

FOR several years Heilbrunn's "General Physiology" has enjoyed a wide circulation as a text for college students and a work of reference for others interested in the subject. The 2nd edition, enlarged and revised to the extent of being virtually a new book, will be of increased usefulness to both classes of readers. The ground covered by it is General Physiology in the broad sense of Bayliss in his "Principles of General Physiology" rather than in the more restricted one of the *Journal of General Physiology*. Included with more conventional material are such up-to-the-minute topics as the electron microscope and the use of tracer elements. Not the least valuable feature of the book is a well-selected list of over 4000 references to the literature accompanying the text in convenient footnote form. The college student, the general reader interested in physiology, and the specialist will all find in it much that is useful and stimulating. M. J.

MEDICAL PHYSICS. Editor-in-Chief, OTTO GLASSER, PH.D., Head, Department of Biophysics, Cleveland Clinic Foundation; Professor of Biophysics, Frank E. Bunts Educational Institute; Consulting Biophysicist, University Hospitals of Cleveland, Cleveland, Ohio. Pp. 1744; many figs. and tables. Chicago: Year Book Publishers, 1944. Price, $18.00.

Is one who first looks over this huge volume to marvel more at the boldness of the publisher who conceived it—a pioneer of its kind—and then published a heavy $18 book in one volume, or at the energy of the Editor who with the aid of 23 Associate Editors and over 200 Collaborators selected and provided the text? It is not surprising that manuscripts were being turned in to the Editor from early 1941 to October, 1943. The Collaborator group includes a number of well-known authorities in their fields, which cover a wide range: Physics, Chemistry, Biology, Physiology, Pathology, Internal Medicine, Surgery, Neurology, Public Health and others too numerous to mention. The 200 or more items found in the Table of Contents are arranged alphabetically as in an encyclopedia. In the Classified Table of Contents, including 24 topics, from Anatomy to Urology, of course the subdivisions do not follow the paginated sequence.

The book "attempts to embody a combination of an *encyclopedia*, sufficiently comprehensive to serve as a reference for all those whose occupations involve any aspects of medical physics; a *textbook*, adequately detailed in exposition to serve students; and a *working instrument*, in which may be found the data necessary for actual application of the principles of physics to medicine. Readers will undoubtedly discover that this volume falls short of the attainment of that ideal." We regret to have to say that the last sentence is only too true, for various reasons that need not be gone into in detail. However, there is more than enough of value in the text as it stands to make it

well worth while; and the same vigorous editing can doubtless correct errors of omission and commission in future editions. And by "errors of commission" it is not intended to mean inaccurate statements; there are many sections that seem unnecessary, even out of place in a work of this kind. As one might expect, some of the articles are inferior (poorly selected, poorly planned, and poorly carried out); but many more, especially if one takes the standing of the author into account, are just the opposite. Medical men coming to the book for information and instruction of a medico-physical nature will as a rule be well satisfied. One has only to compare the first edition of the Encyclopedia Britannica with the eleventh or fourteenth to visualize a far-reaching future for this first venture of its kind in Medical Physics. E. K.

BEHIND THE UNIVERSE: A Doctor's Religion. By LOUIS BERMAN, M.D. Pp. 303. New York: Harper & Brothers, 1943. Price, $2.75.

THE author, an endocrinologist, states that man, the only species cognizant of his place and functions in the universe, will become extinct unless a way is found to end this ever-increasing destruction by his fellows. The remedy offered in this thesis is disclosed in the following chapters on the immortality of ideas, the isolation of individual consciousness, the continuity of the life personality, the brain as the medium of continuity, psychic forces in life history, the creative powers of the unconscious, from the unconscious to the superconscious, a world prepared for life, the universe as a psycho-continuum, the cosmic drive behind consciousness, the living as a multiple split personality, the return to the mystic participation and the God of evolution.

From protoplasm to man, and finally to God, many topics are discussed—a range too great for comprehensive review. We are told how symbiosis—mutualism—is at work between plant and plant, between plant and animal, also between animal and animal. The life of the bee is cited, where though each insect has its own job, all work to maintain "the spirit of the hive." In the case of man, it is claimed that his "chronic unhappiness has been due to the poisonous privacies and destructive discontentments bred of individuation." A universal psychic symbiosis, a mystic participation, and a renaissance of God-consciousness is offered for the salvation of the race. The author's style includes many well-chosen metaphors. Though some may question the soundness of his doctrine, his thesis affords much interesting and stimulating reading. There is no formal bibliography and no index.

N. Y.

NEW BOOKS

Clinical Lectures on the Gallbladder and Bile Ducts. By SAMUEL WEISS, M.D., F.A.C.P., Clinical Professor of Gastroenterology, New York Polyclinic Medical School and Hospital; Gastroenterologist, Jewish Memorial Hospital, New York; Consulting Gastroenterologist, Beth David Hospital, New York, Long Island, etc. Pp. 504; 124 figs.; 21 tables. Chicago: Year Book Publishers, 1944. Price, $5.50.

Der Schwund Tuberkuloser Lungenkavernen. By PROF. DR. WALTER BERBLINGER. Pp. 130; 61 illus. Basel: Benno Schwabe, 1943. Price, 15 Swiss Fr.

The Jews and Medicine. Essays. By HARRY FRIEDENWALD, M.D., D.H.L. (HON.), D.Sc. (HON.), Professor Emeritus of Ophthalmology, Univ. of Maryland. Vols. I and II. Pp. 817; a few figs. Publications of the Institute of the History of Medicine, Johns Hopkins Univ. First series: Monographs, Vols. II and III. Baltimore: Johns Hopkins Press, 1944. Price, $7.50.

The Riddle of Cancer. By CHARLES OBERLING, M.D. Translated by WILLIAM H. WOGLOM, M.D. Pp. 196. New Haven: Yale Univ. Press; London: Oxford Univ. Press, 1944. Price, $3.00.

Vascular Responses in the Extremities of Man in Health and Disease. By DAVID I. ABRAMSON, M.D., F.A.C.P. Pp. 412; 59 figs.; 4 tables. Chicago: Univ. of Chicago Press, 1944. Price, $5.00.

Handbook of Nutrition. A Symposium Prepared Under the Auspices of the Council on Foods and Nutrition of the American Medical Association. Pp. 586; many figures and tables. Chicago: American Medical Association, 1943. Price, $2.50.

History of Miners' Diseases. By GEORGE ROSEN, M.D. Introduction by HENRY E. SIGERIST, M.D. Pp. 490; many figures and tables. New York: Schuman's, 1943. Price, $8.50.

A Bio-Bibliography of Andreas Vesalius. By HARVEY CUSHING, M.D. Preface by JOHN F. FULTON, M.D. Publication No. 6 Historical Library, Yale Medical Library. Pp. 229; 89 figs. New York: Schuman's, 1943. Price, $15.00.

Harvey Cushing Collection of Books and Manuscripts. Publication No. 1 Historical Library, Yale Medical Library. Preface by JOHN F. FULTON, M.D. Pp. 207. New York: Schuman's, 1943. Price, $8.50.

An Atlas of Anatomy. By J. C. BOILEAU GRANT, M.C., M.B., CH.B., F.R.C.S. (EDIN.), Professor of Anatomy in the Univ. of Toronto. Vol. II. Vertebræ and Vertebral Column, Thorax, Head and Neck. Pp. 390; 460 figs. Baltimore: Williams & Wilkins, 1943. Price, $5.00.

The Methodology of Pierre Duhem. By ARMAND LOWINGER. Pp. 184. New York: Columbia Univ. Press, 1941. Price, $2.25.

Surface Chemistry. Edited by FOREST RAY MOULTON. Pp. 160; many figs. and tables. Washington, D. C.: Amer. Assn. for the Advancement of Science, 1943. Price, members, $2.75; to others, $3.25.

Rorschach's Test. 1. Basic Processes. By SAMUEL J. BECK, PH.D., Head of Psychology Laboratory, Department of Neuropsychiatry, Michael Reese Hospital, Chicago; Associate Professor of Psychology, Northwestern Univ. Foreword by WILLARD L. VALENTINE, PH.D., Head of Dept. of Psychology, Northwestern Univ. Pp. 223; many figs. and tables. New York: Grune & Stratton, 1944. Price, $3.50.

Photo-micrography. By R. M. ALLEN. Pp. 265; 50 plates; 175 figs. New York: D. Van Nostrand, 1941. Price, $5.50.

Persistence and Change in Personality Patterns. By KATHERINE ELLIOTT ROBERTS and VIRGINIA VAN DYNE FLEMING. Monographs of the Society for Research in Child Development. Vol. VIII, No. 3 (Serial No. 36). Pp. 206; 26 tables. Washington, D. C.: National Research Council, 1943. Price, $1.50.

NEW EDITIONS

A Text-Book of Pathology. Edited by E. T. BELL, M.D. Contributors: E. T. BELL, M.D., Professor of Pathology, Univ. of Minnesota; B. J. CLAWSON, M.D., Professor of Pathology, Univ. of Minnesota; and M. S. MCCARTNEY, M.D., Associate Professor of Pathology, Univ. of Minnesota. Fifth ed. Pp. 862; 448 figs. (4 color plates). Philadelphia: Lea & Febiger, 1944. Price, $9.50.

Manual of the Diseases of the Eye. By CHARLES H. MAY, M.D., Consulting Ophthalmologist to Bellevue, Mt. Sinai and French Hospitals, New York; Formerly Chief of Clinic and Instructor in Ophthalmology, Medical Department of Columbia Univ.; and Director of the Eye Service at Bellevue Hospital, New York. With the assistance of CHARLES A. PERERA, M.D., Associate in Ophthalmology, College of Physicians and Surgeons, Medical Department of Columbia Univ., New York; Assistant Attending Ophthalmologist, Presbyterian Hospital, New York. New Eighteenth ed. Pp. 520; 387 figs. (32 plates, 93 colored figs.). Baltimore: William Wood, 1943. Price, $4.00.

Laboratory Methods of the United States Army. Edited by JAMES STEVENS SIMMONS, B.S., M.D., PH.D., D.P.H., Sc.D. (HON.); and CLEON J. GENTZKOW, M.D., PH.D. Fifth ed. Pp. 823; 108 tables, 103 figs. (8 color plates). Philadelphia: Lea & Febiger, 1944. Price, $7.50.

Office Endocrinology. By ROBERT B. GREENBLATT, B.A., M.D., C.M., Professor of Experimental Medicine, Univ. of Georgia School of Medicine; Director, Sex Endocrine Clinic, Univ. Hospital, Augusta, Ga. Foreword by G. LOMBARD KELLY, M.D., Dean, Univ. of Georgia School of Medicine. Second ed. Pp. 243; many figs. Springfield, Ill.: Charles C Thomas, 1944. Price, $4.00.

The Microscope. By R. M. ALLEN. Third Printing. Pp. 286; 17 plates; 82 figs. New York: D. Van Nostrand, 1944. Price, $3.00.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

NEW NOTICE TO CONTRIBUTORS AND SUBSCRIBERS

Activated by a directive from the War Production Board, we have changed the size of our type page for the "duration" to effect an economy in the amount of paper used. While there is a smaller number of pages, the amount of material has not been noticeably reduced.

We hope that any unpleasant effect produced by cutting down the margins will be accepted and approved by readers as a temporary war casualty. It is possible that more radical changes will have to be made later, but we are loath to change any more than absolutely necessary, a format that has existed practically unchanged since the Journal began in 1820.

For the balance of the war, 150 reprints will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150. This modification is for the same reason as the change of format, *i. e.*, conservation of paper.

NOTICE TO SUBSCRIBERS AND ADVERTISERS

We desire to secure several copies of the March and May 1943 numbers of this Journal, in order to comply with requests and need for replacements in long library "runs." The war situation has made it impossible to print extra numbers to supply this demand. We would be *very* grateful to anyone who would return to the Publishers any unmutilated copies of these numbers for which they have no further use, and we would be glad to repay postage.